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(73) Patenthaver: **ADENIUM BIOTECH APS, Ole Maaløesvej 3, 2200 København N, Danmark**

(72) Opfinder: **HOEGENHAUG, Hans-Henrik, Kristensen, Kong Valdemarsvej 16, 9999 Ukendt, Danmark**
**MYGIND, Per, Holse, Boegehaven 72, 3500 Værløse, Danmark**
**KRUSE, Thomas, Axel Heides Gade 10, 3. tv, 2300 København S, Danmark**
**SEGURA, Dorotea Raventos, Skovridervej 1, 2960 Rungsted Kyst, Danmark**
**SANDVANG, Dorthe, Kollensoevej 8, 3550 Slangerup, Danmark**
**NEVE, Soren, Ellevaenget 4, 2880 Bagsværd, Danmark**

(74) Fuldmægtig i Danmark: **ZBM PATENTS ApS, Fruebjergvej 3, 2100 København Ø, Danmark**

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**Fortsættes ...**

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# DESCRIPTION

**Reference to a Sequence Listing**

**[0001]** This application contains a Sequence Listing in computer readable form, which is incorporated herein by reference.

**Background of the Invention**

**Field of the Invention**

**[0002]** The present invention relates to variants of an antimicrobial peptide, polynucleotides encoding the variants, methods of producing the variants, and methods of using the variants.

**Description of the Related Art**

**[0003]** Several classes of antimicrobial peptides (AMPs) have been described in literature, examples of which include defensins and alpha-helical peptides.

**[0004]** The present invention provides variants of an antimicrobial peptide isolated from *Arenicola marina,* and described in WO 2007/023163.

**[0005]** The variant antimicrobial peptides of the present invention exhibit improved antimicrobial activity as compared to the parent antimicrobial peptide. In particular, the variants exhibit improved antimicrobial activity in the presence of serum and blood proteins. Another advantage of the variant peptides of the invention is a reduced protein binding e.g. to serum and blood proteins, which results in an improved bioavailability as compared to the parent antimicrobial peptide.

**Summary of the Invention**

**[0006]** The present invention relates to isolated variants of an antimicrobial peptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 72 and SEQ ID NO: 350, wherein the variant has antimicrobial activity.

**[0007]** The present invention also relates to isolated polynucleotides encoding the variants; nucleic acid constructs, vectors, and host cells comprising the polynucleotides; and methods of producing the variants.

**[0008]** The present invention also relates to a method of treating a microbial infection using the variants of the invention; and use of variants for manufacturing a medicament for the treatment of a microbial infection.

**Detailed Description of the Invention**

**[0009]** The present invention relates to isolated variants of an antimicrobial peptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 72 and SEQ ID NO: 350, wherein the variant has antimicrobial activity.

**Polynucleotides**

**[0010]** The present invention also relates to isolated polynucleotides that encode any of the variants of the present invention.

**Nucleic Acid Constructs**

**[0011]** The present invention also relates to nucleic acid constructs comprising a polynucleotide encoding a variant of the present invention operably linked to one or more (several) control sequences that direct the expression of the coding sequence in a suitable host cell under conditions compatible with the control sequences.

**[0012]** A polynucleotide may be manipulated in a variety of ways to provide for expression of a variant. Manipulation of the polynucleotide prior to its insertion into a vector may be desirable or necessary depending on the expression vector. The techniques for modifying polynucleotides utilizing recombinant DNA methods are well known in the art.

**[0013]** The control sequence may be a promoter sequence, which is recognized by a host cell for expression of the polynucleotide. The promoter sequence contains transcriptional control sequences that mediate the expression of the variant. The promoter may be any nucleic acid sequence that shows transcriptional activity in the host cell including mutant, truncated, and hybrid promoters, and may be obtained from genes encoding extracellular or intracellular peptides either homologous or heterologous to the host cell.

**[0014]** Examples of suitable promoters for directing the transcription of the nucleic acid constructs of the present invention in a bacterial host cell are the promoters obtained from the *Bacillus amyloliquefaciens* alpha-amylase gene (*amyQ*), *Bacillus licheniformis* alpha-amylase gene (*amyL*), *Bacillus licheniformis* penicillinase gene (*penP*), *Bacillus stearothermophilus* maltogenic amylase gene (*amyM*), *Bacillus subtilis* levansucrase gene (*sacB*), *Bacillus subtilis xylA* and *xylB* genes, *E. coli lac* operon, *Streptomyces coelicolor* agarase gene (*dagA*), and prokaryotic beta-lactamase gene (Villa-Kamaroff et al., 1978, Proc. Natl. Acad. Sci. USA 75: 3727-3731), as well as the *tac* promoter (DeBoer et al., 1983, Proc. Natl. Acad. Sci. USA 80: 21-25). Further promoters are described in "Useful proteins from recombinant bacteria" in Gilbert et al., 1980, Scientific American 242: 74-94; and in Sambrook *et al.,* 1989, *supra.*

**[0015]** Examples of suitable promoters for directing the transcription of the nucleic acid constructs of the present invention in a filamentous fungal host cell are the promoters obtained from the genes for *Aspergillus nidulans* acetamidase, *Aspergillus niger* neutral alpha-amylase, *Aspergillus niger* acid stable alpha-amylase, *Aspergillus niger* or *Aspergillus awamori* glucoamylase (*glaA*), *Aspergillus oryzae* TAKA amylase, *Aspergillus oryzae* alkaline protease, *Aspergillus oryzae* triose phosphate isomerase, *Fusarium oxysporum* trypsin-like protease (WO 96/00787), *Fusarium venenatum* amyloglucosidase (WO 00/56900), *Fusarium venenatum* Daria (WO 00/56900), *Fusarium venenatum* Quinn (WO 00/56900), *Rhizomucor*

*miehei* lipase, *Rhizomucor miehei* aspartic proteinase, *Trichoderma reesei* beta-glucosidase, *Trichoderma reesei* cellobiohydrolase I, *Trichoderma reesei* cellobiohydrolase II, *Trichoderma reesei* endoglucanase I, *Trichoderma reesei* endoglucanase II, *Trichoderma reesei* endoglucanase III, *Trichoderma reesei* endoglucanase IV, *Trichoderma reesei* endoglucanase V, *Trichoderma reesei* xylanase I, *Trichoderma reesei* xylanase II, *Trichoderma reesei* beta-xylosidase, as well as the NA2-tpi promoter (a modified promoter including a gene encoding a neutral alpha-amylase in *Aspergilli* in which the untranslated leader has been replaced by an untranslated leader from a gene encoding triose phosphate isomerase in *Aspergilli;* non-limiting examples include modified promoters including the gene encoding neutral alpha-amylase in *Aspergillus niger* in which the untranslated leader has been replaced by an untranslated leader from the gene encoding triose phosphate isomerase in *Aspergillus nidulans* or *Aspergillus oryzae*); and mutant, truncated, and hybrid promoters thereof.

**[0016]** In a yeast host, useful promoters are obtained from the genes for *Saccharomyces cerevisiae* enolase (ENO-1), *Saccharomyces cerevisiae* galactokinase (GAL1), *Saccharomyces cerevisiae* alcohol dehydrogenase/glyceraldehyde-3-phosphate dehydrogenase (ADH1, ADH2/GAP), *Saccharomyces cerevisiae* triose phosphate isomerase (TPI), *Saccharomyces cerevisiae* metallothionein (CUP1), and *Saccharomyces cerevisiae* 3-phosphoglycerate kinase. Other useful promoters for yeast host cells are described by Romanos et al., 1992, Yeast 8: 423-488.

**[0017]** The control sequence may also be a suitable transcription terminator sequence, which is recognized by a host cell to terminate transcription. The terminator sequence is operably linked to the 3'-terminus of the polynucleotide encoding the variant. Any terminator that is functional in the host cell may be used.

**[0018]** Preferred terminators for filamentous fungal host cells are obtained from the genes for *Aspergillus nidulans* anthranilate synthase, *Aspergillus niger* alpha-glucosidase, *Aspergillus niger* glucoamylase, *Aspergillus oryzae* TAKA amylase, and *Fusarium oxysporum* trypsin-like protease.

**[0019]** Preferred terminators for yeast host cells are obtained from the genes for *Saccharomyces cerevisiae* enolase, *Saccharomyces cerevisiae* cytochrome C (CYC1), and *Saccharomyces cerevisiae* glyceraldehyde-3-phosphate dehydrogenase. Other useful terminators for yeast host cells are described by Romanos *et al.,* 1992, *supra.*

**[0020]** The control sequence may also be a suitable leader sequence, a nontranslated region of an mRNA that is important for translation by the host cell. The leader sequence is operably linked to the 5'-terminus of the polynucleotide encoding the variant. Any leader sequence that is functional in the host cell may be used.

**[0021]** Preferred leaders for filamentous fungal host cells are obtained from the genes for *Aspergillus oryzae* TAKA amylase and *Aspergillus nidulans* triose phosphate isomerase. Suitable leaders for yeast host cells are obtained from the genes for *Saccharomyces cerevisiae* enolase (ENO-1), *Saccharomyces cerevisiae* 3-phosphoglycerate kinase, *Saccharomyces cerevisiae* alpha-factor, and *Saccharomyces cerevisiae* alcohol dehydrogenase/glyceraldehyde-3-phosphate dehydrogenase (ADH2/GAP).

**[0022]** The control sequence may also be a polyadenylation sequence, a sequence operably linked to the 3'-terminus of the variant-encoding sequence and, when transcribed, is recognized by the host cell as a signal to add polyadenosine residues to transcribed mRNA. Any polyadenylation sequence that is functional in the host cell may be used.

**[0023]** Preferred polyadenylation sequences for filamentous fungal host cells are obtained from the genes

for *Aspergillus nidulans* anthranilate synthase, *Aspergillus niger* glucoamylase, *Aspergillus niger* alpha-glucosidase, *Aspergillus oryzae* TAKA amylase, and *Fusarium oxysporum* trypsin-like protease.

**[0024]** Useful polyadenylation sequences for yeast host cells are described by Guo and Sherman, 1995, Mol. Cellular Biol. 15: 5983-5990.

**[0025]** The control sequence may also be a signal peptide coding region that encodes a signal peptide linked to the N-terminus of a variant and directs the variant into the cell's secretory pathway. The 5'-end of the coding sequence of the polynucleotide may inherently contain a signal peptide coding region naturally linked in translation reading frame with the segment of the coding region that encodes the variant. Alternatively, the 5'-end of the coding sequence may contain a signal peptide coding region that is foreign to the coding sequence. The foreign signal peptide coding region may be required where the coding sequence does not naturally contain a signal peptide coding region. Alternatively, the foreign signal peptide coding region may simply replace the natural signal peptide coding region in order to enhance secretion of the variant. However, any signal peptide coding region that directs the expressed variant into the secretory pathway of a host cell may be used.

**[0026]** Effective signal peptide coding sequences for bacterial host cells are the signal peptide coding sequences obtained from the genes for *Bacillus* NCIB 11837 maltogenic amylase, *Bacillus licheniformis* subtilisin, *Bacillus licheniformis* beta-lactamase, *Bacillus stearothermophilus* alpha-amylase, *Bacillus stearothermophilus* neutral proteases (*nprT, nprS, nprM*), and *Bacillus subtilis prsA.* Further signal peptides are described by Simonen and Palva, 1993, Microbiological Reviews 57: 109-137.

**[0027]** Effective signal peptide coding sequences for filamentous fungal host cells are the signal peptide coding sequences obtained from the genes for *Aspergillus niger* neutral amylase, *Aspergillus niger* glucoamylase, *Aspergillus oryzae* TAKA amylase, *Humicola insolens* cellulase, *Humicola insolens* endoglucanase V, *Humicola lanuginosa* lipase, and *Rhizomucor miehei* aspartic proteinase.

**[0028]** Useful signal peptides for yeast host cells are obtained from the genes for *Saccharomyces cerevisiae* alpha-factor and *Saccharomyces cerevisiae* invertase. Other useful signal peptide coding sequences are described by Romanos *et al.,* 1992, *supra.*

**[0029]** The control sequence may also be a propeptide coding region that encodes a propeptide positioned at the N-terminus of a variant. The resultant peptide is known as a proenzyme or propeptide (or a zymogen in some cases). A propeptide is generally inactive and can be converted to an active peptide by catalytic or autocatalytic cleavage of the propeptide from the propeptide. The propeptide coding region may be obtained from the genes for *Bacillus subtilis* alkaline protease (*aprE*), *Bacillus subtilis* neutral protease (*nprT*), *Myceliophthora thermophila* laccase (WO 95/33836), *Rhizomucor miehei* aspartic proteinase, and *Saccharomyces cerevisiae* alpha-factor.

**[0030]** Where both signal peptide and propeptide regions are present at the N-terminus of a variant, the propeptide region is positioned next to the N-terminus of the variant and the signal peptide region is positioned next to the N-terminus of the propeptide region.

**[0031]** It may also be desirable to add regulatory sequences that allow the regulation of the expression of the variant relative to the growth of the host cell. Examples of regulatory systems are those that cause the expression of the gene to be turned on or off in response to a chemical or physical stimulus, including the presence of a regulatory compound. Regulatory systems in prokaryotic systems include the *lac, tac,* and *trp* operator systems. In yeast, the ADH2 system or GAL1 system may be used. In filamentous fungi, the

*Aspergillus niger* glucoamylase promoter, *Aspergillus oryzae* TAKA alpha-amylase promoter, and *Aspergillus oryzae* glucoamylase promoter may be used. Other examples of regulatory sequences are those that allow for gene amplification. In eukaryotic systems, these regulatory sequences include the dihydrofolate reductase gene that is amplified in the presence of methotrexate, and the metallothionein genes that are amplified with heavy metals. In these cases, the polynucleotide encoding the variant would be operably linked with the regulatory sequence.

**Expression Vectors**

**[0032]** The present invention also relates to recombinant expression vectors comprising a polynucleotide of the present invention, a promoter, and transcriptional and translational stop signals. The various nucleotide and control sequences may be joined together to produce a recombinant expression vector that may include one or more (several) convenient restriction sites to allow for insertion or substitution of the polynucleotide encoding the variant at such sites. Alternatively, the polynucleotide may be expressed by inserting the polynucleotide or a nucleic acid construct comprising the polynucleotide into an appropriate vector for expression. In creating the expression vector, the coding sequence is located in the vector so that the coding sequence is operably linked with the appropriate control sequences for expression.

**[0033]** The recombinant expression vector may be any vector (*e.g.,* a plasmid or virus) that can be conveniently subjected to recombinant DNA procedures and can bring about the expression of the polynucleotide. The choice of the vector will typically depend on the compatibility of the vector with the host cell into which the vector is to be introduced. The vector may be a linear or closed circular plasmid.

**[0034]** The vector may be an autonomously replicating vector, *i.e.,* a vector that exists as an extrachromosomal entity, the replication of which is independent of chromosomal replication, *e.g.,* a plasmid, an extrachromosomal element, a minichromosome, or an artificial chromosome. The vector may contain any means for assuring self-replication. Alternatively, the vector may be one that, when introduced into the host cell, is integrated into the genome and replicated together with the chromosome(s) into which it has been integrated. Furthermore, a single vector or plasmid or two or more vectors or plasmids that together contain the total DNA to be introduced into the genome of the host cell, or a transposon, may be used.

**[0035]** The vector preferably contains one or more (several) selectable markers that permit easy selection of transformed, transfected, transduced, or the like cells. A selectable marker is a gene the product of which provides for biocide or viral resistance, resistance to heavy metals, prototrophy to auxotrophs, and the like.

**[0036]** Examples of bacterial selectable markers are the *dal* genes from *Bacillus licheniformis* or *Bacillus subtilis,* or markers that confer antibiotic resistance such as ampicillin, chloramphenicol, kanamycin, or tetracycline resistance. Suitable markers for yeast host cells are ADE2, HIS3, LEU2, LYS2, MET3, TRP1, and URA3. Selectable markers for use in a filamentous fungal host cell include, but are not limited to, amdS (acetamidase), *argB* (ornithine carbamoyltransferase), *bar* (phosphinothricin acetyltransferase), *hph* (hygromycin phosphotransferase), *niaD* (nitrate reductase), *pyrG* (orotidine-5'-phosphate decarboxylase), *sC* (sulfate adenyltransferase), and *trpC* (anthranilate synthase), as well as equivalents thereof. Preferred for use in an *Aspergillus* cell are the *amdS* and *pyrG* genes of *Aspergillus nidulans* or *Aspergillus oryzae* and the *bar* gene of *Streptomyces hygroscopicus.*

**[0037]** The vector preferably contains an element(s) that permits integration of the vector into the host

cell's genome or autonomous replication of the vector in the cell independent of the genome.

**[0038]** For integration into the host cell genome, the vector may rely on the polynucleotide's sequence encoding the variant or any other element of the vector for integration into the genome by homologous or nonhomologous recombination. Alternatively, the vector may contain additional nucleotide sequences for directing integration by homologous recombination into the genome of the host cell at a precise location(s) in the chromosome(s). To increase the likelihood of integration at a precise location, the integrational elements should contain a sufficient number of nucleic acids, such as 100 to 10,000 base pairs, 400 to 10,000 base pairs, and 800 to 10,000 base pairs, which have a high degree of identity to the corresponding target sequence to enhance the probability of homologous recombination. The integrational elements may be any sequence that is homologous with the target sequence in the genome of the host cell. Furthermore, the integrational elements may be non-encoding or encoding nucleotide sequences. On the other hand, the vector may be integrated into the genome of the host cell by non-homologous recombination.

**[0039]** For autonomous replication, the vector may further comprise an origin of replication enabling the vector to replicate autonomously in the host cell in question. The origin of replication may be any plasmid replicator mediating autonomous replication that functions in a cell. The term "origin of replication" or "plasmid replicator" means a nucleotide sequence that enables a plasmid or vector to replicate *in vivo.*

**[0040]** Examples of bacterial origins of replication are the origins of replication of plasmids pBR322, pUC19, pACYC177, and pACYC184 permitting replication in *E. coli,* and pUB110, pE194, pTA1060, and pAMβ1 permitting replication in *Bacillus.*

**[0041]** Examples of origins of replication for use in a yeast host cell are the 2 micron origin of replication, ARS1, ARS4, the combination of ARS1 and CEN3, and the combination of ARS4 and CEN6.

**[0042]** Examples of origins of replication useful in a filamentous fungal cell are AMA1 and ANS1 (Gems et al., 1991, Gene 98: 61-67; Cullen et al., 1987, Nucleic Acids Res. 15: 9163-9175; WO 00/24883). Isolation of the AMA1 gene and construction of plasmids or vectors comprising the gene can be accomplished according to the methods disclosed in WO 00/24883.

**[0043]** More than one copy of a polynucleotide of the present invention may be inserted into the host cell to increase production of a variant. An increase in the copy number of the polynucleotide can be obtained by integrating at least one additional copy of the sequence into the host cell genome or by including an amplifiable selectable marker gene with the polynucleotide where cells containing amplified copies of the selectable marker gene, and thereby additional copies of the polynucleotide, can be selected for by cultivating the cells in the presence of the appropriate selectable agent.

**[0044]** The procedures used to ligate the elements described above to construct the recombinant expression vectors of the present invention are well known to one skilled in the art (see, *e.g.,* Sambrook *et al.,* 1989, *supra*) to obtain substantially pure variants.

**Host Cells**

**[0045]** The present invention also relates to recombinant host cells, comprising a polynucleotide of the present invention operably linked to one or more (several) control sequences that direct the production of a variant of the present invention. A construct or vector comprising a polynucleotide is introduced into a

host cell so that the construct or vector is maintained as a chromosomal integrant or as a self-replicating extra-chromosomal vector as described earlier. The term "host cell" encompasses any progeny of a parent cell that is not identical to the parent cell due to mutations that occur during replication. The choice of a host cell will to a large extent depend upon the gene encoding the variant and its source.

**[0046]** The host cell may be any cell useful in the recombinant production of a variant, *e.g.,* a prokaryote or a eukaryote.

**[0047]** The prokaryotic host cell may be any gram-positive or gram-negative bacterium. Gram-positive bacteria include, but are not limited to, *Bacillus, Clostridium, Enterococcus, Geobacillus, Lactobacillus, Lactococcus, Oceanobacillus, Staphylococcus, Streptococcus,* and *Streptomyces.* Gram-negative bacteria include, but are not limited to, *Campylobacter, E. coli, Flavobacterium, Fusobacterium, Helicobacter, Ilyobacter, Neisseria, Pseudomonas, Salmonella,* and *Ureaplasma.*

**[0048]** The bacterial host cell may be any Bacillus cell, including, but not limited to, Bacillus alkalophilus, Bacillus amyloliquefaciens, Bacillus brevis, Bacillus circulans, Bacillus clausii, Bacillus coagulans, Bacillus firmus, Bacillus lautus, Bacillus lentus, Bacillus licheniformis, Bacillus megaterium, Bacillus pumilus, Bacillus stearothermophilus, Bacillus subtilis, and Bacillus thuringiensis cells.

**[0049]** The bacterial host cell may also be any Streptococcus cell, including, but not limited to, Streptococcus equisimilis, Streptococcus pyogenes, Streptococcus uberis, and Streptococcus equi subsp. Zooepidemicus cells.

**[0050]** The bacterial host cell may also be any Streptomyces cell, including, but not limited to, Streptomyces achromogenes, Streptomyces avermitilis, Streptomyces coelicolor, Streptomyces griseus, and Streptomyces lividans cells.

**[0051]** The introduction of DNA into a *Bacillus* cell may, for instance, be effected by protoplast transformation (see, *e.g.,* Chang and Cohen, 1979, Mol. Gen. Genet. 168: 111-115), by using competent cells (see, *e.g.,* Young and Spizizen, 1961, J. Bacteriol. 81: 823-829, or Dubnau and Davidoff-Abelson, 1971, J. Mol. Biol. 56: 209-221), by electroporation (see, *e.g.,* Shigekawa and Dower, 1988, Biotechniques 6: 742-751), or by conjugation (see, *e.g.,* Koehler and Thorne, 1987, J. Bacteriol. 169: 5271-5278). The introduction of DNA into an *E. coli cell* may, for instance, be effected by protoplast transformation (see, *e.g.,* Hanahan, 1983, J. Mol. Biol. 166: 557-580) or electroporation (see, *e.g.,* Dower et al., 1988, Nucleic Acids Res. 16: 6127-6145). The introduction of DNA into a *Streptomyces* cell may, for instance, be effected by protoplast transformation and electroporation (see, *e.g.,* Gong et al., 2004, Folia Microbiol. (Praha) 49: 399-405), by conjugation (see, *e.g.,* Mazodier et al., 1989, J. Bacteriol. 171: 3583-3585), or by transduction (see, *e.g.,* Burke et al., 2001, Proc. Natl. Acad. Sci. USA 98: 6289-6294 ). The introduction of DNA into a *Pseudomonas* cell may, for instance, be effected by electroporation (see, *e.g.,* Choi et al., 2006, J. Microbiol. Methods 64: 391-397) or by conjugation (see, *e.g.,* Pinedo and Smets, 2005, Appl. Environ. Microbiol. 71: 51-57). The introduction of DNA into a *Streptococcus* cell may, for instance, be effected by natural competence (see, *e.g.,* Perry and Kuramitsu, 1981, Infect. Immun. 32: 1295-1297), by protoplast transformation (see, *e.g.,* Catt and Jollick, 1991, Microbios 68: 189-2070, by electroporation (see, *e.g.,* Buckley et al., 1999, Appl. Environ. Microbiol. 65: 3800-3804) or by conjugation (see, *e.g.,* Clewell, 1981, Microbiol. Rev. 45: 409-436). However, any method known in the art for introducing DNA into a host cell can be used.

**[0052]** The host cell may also be a eukaryote, such as a mammalian, insect, plant, or fungal cell.

**[0053]** The host cell may be a fungal cell. "Fungi" as used herein includes the phyla Ascomycota,

Basidiomycota, Chytridiomycota, and Zygomycota as well as the Oomycota and all mitosporic fungi (as defined by Hawksworth et al., In, Ainsworth and Bisby's Dictionary of The Fungi, 8th edition, 1995, CAB International, University Press, Cambridge, UK).

**[0054]** The fungal host cell may be a yeast cell. "Yeast" as used herein includes ascosporogenous yeast (Endomycetales), basidiosporogenous yeast, and yeast belonging to the Fungi Imperfecti (Blastomycetes). Since the classification of yeast may change in the future, for the purposes of this invention, yeast shall be defined as described in Biology and Activities of Yeast (Skinner, F.A., Passmore, S.M., and Davenport, R.R., eds, Soc. App. Bacteriol. Symposium Series No. 9, 1980).

**[0055]** The yeast host cell may be a Candida, Hansenula, Kluyveromyces, Pichia, Saccharomyces, Schizosaccharomyces, or Yarrowia cell such as a Kluyveromyces lactis, Saccharomyces carlsbergensis, Saccharomyces cerevisiae, Saccharomyces diastaticus, Saccharomyces douglasii, Saccharomyces kluyveri, Saccharomyces norbensis, Saccharomyces oviformis, or Yarrowia lipolytica cell.

**[0056]** The fungal host cell may be a filamentous fungal cell. "Filamentous fungi" include all filamentous forms of the subdivision Eumycota and Oomycota (as defined by Hawksworth *et al.,* 1995, *supra*). The filamentous fungi are generally characterized by a mycelial wall composed of chitin, cellulose, glucan, chitosan, mannan, and other complex polysaccharides. Vegetative growth is by hyphal elongation and carbon catabolism is obligately aerobic. In contrast, vegetative growth by yeasts such as *Saccharomyces cerevisiae* is by budding of a unicellular thallus and carbon catabolism may be fermentative.

**[0057]** The filamentous fungal host cell may be an Acremonium, Aspergillus, Aureobasidium, Bjerkandera, Ceriporiopsis, Chrysosporium, Coprinus, Coriolus, Cryptococcus, Filibasidium, Fusarium, Humicola, Magnaporthe, Mucor, Myceliophthora, Neocallimastix, Neurospora, Paecilomyces, Penicillium, Phanerochaete, Phlebia, Piromyces, Pleurotus, Schizophyllum, Talaromyces, Thermoascus, Thielavia, Tolypocladium, Trametes, or Trichoderma cell.

**[0058]** For example, the filamentous fungal host cell may be an Aspergillus awamori, Aspergillus foetidus, Aspergillus fumigatus, Aspergillus japonicus, Aspergillus nidulans, Aspergillus niger, Aspergillus oryzae, Bjerkandera adusta, Ceriporiopsis aneirina, Ceriporiopsis caregiea, Ceriporiopsis gilvescens, Ceriporiopsis pannocinta, Ceriporiopsis rivulosa, Ceriporiopsis subrufa, Ceriporiopsis subvermispora, Chrysosporium inops, Chrysosporium keratinophilum, Chrysosporium lucknowense, Chrysosporium merdarium, Chrysosporium pannicola, Chrysosporium queenslandicum, Chrysosporium tropicum, Chrysosporium zonatum, Coprinus cinereus, Coriolus hirsutus, Fusarium bactridioides, Fusarium cerealis, Fusarium crookwellense, Fusarium culmorum, Fusarium graminearum, Fusarium graminum, Fusarium heterosporum, Fusarium negundi, Fusarium oxysporum, Fusarium reticulatum, Fusarium roseum, Fusarium sambucinum, Fusarium sarcochroum, Fusarium sporotrichioides, Fusarium sulphureum, Fusarium torulosum, Fusarium trichothecioides, Fusarium venenatum, Humicola insolens, Humicola lanuginosa, Mucor miehei, Myceliophthora thermophila, Neurospora crassa, Penicillium purpurogenum, Phanerochaete chrysosporium, Phlebia radiata, Pleurotus eryngii, Thielavia terrestris, Trametes villosa, Trametes versicolor, Trichoderma harzianum, Trichoderma koningii, Trichoderma longibrachiatum, Trichoderma reesei, or Trichoderma viride cell.

**[0059]** Fungal cells may be transformed by a process involving protoplast formation, transformation of the protoplasts, and regeneration of the cell wall in a manner known *per se.* Suitable procedures for transformation of *Aspergillus* and *Trichoderma* host cells are described in EP 238023 and Yelton et al., 1984, Proc. Natl. Acad. Sci. USA 81: 1470-1474. Suitable methods for transforming *Fusarium* species are described by Malardier et al., 1989, Gene 78: 147-156, and WO 96/00787. Yeast may be transformed

using the procedures described by Becker and Guarente, In Abelson, J.N. and Simon, M.I., editors, Guide to Yeast Genetics and Molecular Biology, Methods in Enzymology, Volume 194, pp 182-187, Academic Press, Inc., New York; Ito et al., 1983, J. Bacteriol. 153: 163; and Hinnen et al., 1978, Proc. Natl. Acad. Sci. USA 75: 1920.

**Methods of Production**

**[0060]** The present invention also relates to methods of producing a variant, comprising: (a) cultivating a host cell of the present invention under conditions suitable for the expression of the variant; and (b) recovering the variant.

**[0061]** The host cells are cultivated in a nutrient medium suitable for production of the variant using methods known in the art. For example, the cell may be cultivated by shake flask cultivation, or small-scale or large-scale fermentation (including continuous, batch, fed-batch, or solid state fermentations) in laboratory or industrial fermentors performed in a suitable medium and under conditions allowing the peptide to be expressed and/or isolated. The cultivation takes place in a suitable nutrient medium comprising carbon and nitrogen sources and inorganic salts, using procedures known in the art. Suitable media are available from commercial suppliers or may be prepared according to published compositions (*e.g.,* in catalogues of the American Type Culture Collection). If the variant is secreted into the nutrient medium, the variant can be recovered directly from the medium. If the variant is not secreted, it can be recovered from cell lysates.

**[0062]** The variant may be detected using methods known in the art that are specific for the variants. These detection methods may include use of specific antibodies, formation of an enzyme product, or disappearance of an enzyme substrate. For example, an enzyme assay may be used to determine the activity of the variant.

**[0063]** The variant may be recovered by methods known in the art. For example, the variant may be recovered from the nutrient medium by conventional procedures including, but not limited to, collection, centrifugation, filtration, extraction, spray-drying, evaporation, or precipitation.

**[0064]** The variant may be purified by a variety of procedures known in the art including, but not limited to, chromatography (*e.g.,* ion exchange, affinity, hydrophobic, chromatofocusing, and size exclusion), electrophoretic procedures (*e.g.,* preparative isoelectric focusing), differential solubility (*e.g.,* ammonium sulfate precipitation), SDS-PAGE, or extraction (see, *e.g.,* Protein Purification, J.-C. Janson and Lars Ryden, editors, VCH Publishers, New York, 1989) to obtain substantially pure variants.

**[0065]** In an alternative aspect, the variant is not recovered, but rather a host cell of the present invention expressing a variant is used as a source of the variant.

***In vitro* synthesis**

**[0066]** The polypeptides of the invention may also be prepared by *in vitro* synthesis, using conventional methods as known in the art. Various commercial synthetic apparatuses are available, for example automated synthesizers by Applied Biosystems Inc., Beckman, etc. By using synthesizers, naturally occurring amino acids may be substituted with unnatural amino acids, particularly D-isomers (or D-forms) e.g. D-alanine and D-isoleucine, diastereoisomers, side chains having different lengths or functionalities,

and the like. The particular sequence and the manner of preparation will be determined by convenience, economics, purity required, and the like.

**[0067]** Chemical linking may be provided to various peptides or proteins comprising convenient functionalities for bonding, such as amino groups for amide or substituted amine formation, e.g. reductive amination, thiol groups for thioether or disulfide formation, carboxyl groups for amide formation, and the like.

**[0068]** If desired, various groups may be introduced into the peptide during synthesis or during expression, which allow for linking to other molecules or to a surface. Thus cysteines can be used to make thioethers, histidines for linking to a metal ion complex, carboxyl groups for forming amides or esters, amino groups for forming amides, and the like.

**[0069]** The polypeptides may also be isolated and purified in accordance with conventional methods of recombinant synthesis. A lysate may be prepared of the expression host and the lysate purified using HPLC, exclusion chromatography, gel electrophoresis, affinity chromatography, or other purification technique. For the most part, the compositions which are used will comprise at least 20% by weight of the desired product, more usually at least about 75% by weight, preferably at least about 95% by weight, and for therapeutic purposes, usually at least about 99.5% by weight, in relation to contaminants related to the method of preparation of the product and its purification. Usually, the percentages will be based upon total protein.

**Plants**

**[0070]** The present disclosure also relates to plants, *e.g.,* a transgenic plant, plant part, or plant cell, comprising a polynucleotide of the present invention so as to express and produce the variant in recoverable quantities. The variant may be recovered from the plant or plant part. Alternatively, the plant or plant part containing the variant may be used as such for improving the quality of a food or feed, *e.g.,* improving nutritional value, palatability, and rheological properties, or to destroy an antinutritive factor.

**[0071]** The transgenic plant can be dicotyledonous (a dicot) or monocotyledonous (a monocot). Examples of monocot plants are grasses, such as meadow grass (blue grass, Poa), forage grass such as Festuca, Lolium, temperate grass, such as Agrostis, and cereals, *e.g.,* wheat, oats, rye, barley, rice, sorghum, and maize (corn).

**[0072]** Examples of dicot plants are tobacco, legumes, such as lupins, potato, sugar beet, pea, bean and soybean, and cruciferous plants (family Brassicaceae), such as cauliflower, rape seed, and the closely related model organism *Arabidopsis thaliana.*

**[0073]** Examples of plant parts are stem, callus, leaves, root, fruits, seeds, and tubers as well as the individual tissues comprising these parts, *e.g.,* epidermis, mesophyll, parenchyme, vascular tissues, meristems. Specific plant cell compartments, such as chloroplasts, apoplasts, mitochondria, vacuoles, peroxisomes and cytoplasm are also considered to be a plant part. Furthermore, any plant cell, whatever the tissue origin, is considered to be a plant part. Likewise, plant parts such as specific tissues and cells isolated to facilitate the utilization of the invention are also considered plant parts, *e.g.,* embryos, endosperms, aleurone and seeds coats.

**[0074]** Also included within the scope of the present disclosure are the progeny of such plants, plant parts,

and plant cells.

**[0075]** The transgenic plant or plant cell expressing a variant may be constructed in accordance with methods known in the art. In short, the plant or plant cell is constructed by incorporating one or more (several) expression constructs encoding a variant into the plant host genome or chloroplast genome and propagating the resulting modified plant or plant cell into a transgenic plant or plant cell.

**[0076]** The expression construct is conveniently a nucleic acid construct that comprises a polynucleotide encoding a variant operably linked with appropriate regulatory sequences required for expression of the polynucleotide in the plant or plant part of choice. Furthermore, the expression construct may comprise a selectable marker useful for identifying plant cells into which the expression construct has been integrated and DNA sequences necessary for introduction of the construct into the plant in question (the latter depends on the DNA introduction method to be used).

**[0077]** The choice of regulatory sequences, such as promoter and terminator sequences and optionally signal or transit sequences, is determined, for example, on the basis of when, where, and how the variant is desired to be expressed. For instance, the expression of the gene encoding a variant may be constitutive or inducible, or may be developmental, stage or tissue specific, and the gene product may be targeted to a specific tissue or plant part such as seeds or leaves. Regulatory sequences are, for example, described by Tague et al., 1988, Plant Physiol. 86: 506.

**[0078]** For constitutive expression, the 35S-CaMV, the maize ubiquitin 1, and the rice actin 1 promoter may be used (Franck et al., 1980, Cell 21: 285-294; Christensen et al., 1992, Plant Mol. Biol. 18: 675-689; Zhang et al., 1991, Plant Cell 3: 1155-1165). Organ-specific promoters may be, for example, a promoter from storage sink tissues such as seeds, potato tubers, and fruits (Edwards and Coruzzi, 1990, Ann. Rev. Genet. 24: 275-303), or from metabolic sink tissues such as meristems (Ito et al., 1994, Plant Mol. Biol. 24: 863-878), a seed specific promoter such as the glutelin, prolamin, globulin, or albumin promoter from rice (Wu et al., 1998, Plant Cell Physiol. 39: 885-889), a *Vicia faba* promoter from the legumin B4 and the unknown seed protein gene from *Vicia faba* (Conrad et al., 1998, J. Plant Physiol. 152: 708-711), a promoter from a seed oil body protein (Chen et al., 1998, Plant Cell Physiol. 39: 935-941), the storage protein *napA* promoter from *Brassica napus,* or any other seed specific promoter known in the art, *e.g.,* as described in WO 91/14772. Furthermore, the promoter may be a leaf specific promoter such as the *rbcs* promoter from rice or tomato (Kyozuka et al., 1993, Plant Physiol. 102: 991-1000), the chlorella virus adenine methyltransferase gene promoter (Mitra and Higgins, 1994, Plant Mol. Biol. 26: 85-93), the *aldP* gene promoter from rice (Kagaya et al., 1995, Mol. Gen. Genet. 248: 668-674), or a wound inducible promoter such as the potato *pin2* promoter (Xu et al., 1993, Plant Mol. Biol. 22: 573-588). Likewise, the promoter may inducible by abiotic treatments such as temperature, drought, or alterations in salinity or induced by exogenously applied substances that activate the promoter, *e.g.,* ethanol, oestrogens, plant hormones such as ethylene, abscisic acid, and gibberellic acid, and heavy metals.

**[0079]** A promoter enhancer element may also be used to achieve higher expression of a variant in the plant. For instance, the promoter enhancer element may be an intron that is placed between the promoter and the polynucleotide encoding a variant. For instance, Xu *et al.,* 1993, *supra,* disclose the use of the first intron of the rice actin 1 gene to enhance expression.

**[0080]** The selectable marker gene and any other parts of the expression construct may be chosen from those available in the art.

**[0081]** The nucleic acid construct is incorporated into the plant genome according to conventional techniques known in the art, including *Agrobacterium*-mediated transformation, virus-mediated

transformation, microinjection, particle bombardment, biolistic transformation, and electroporation (Gasser et al., 1990, Science 244: 1293; Potrykus, 1990, Bio/Technology 8: 535; Shimamoto et al., 1989, Nature 338: 274).

**[0082]** Presently, *Agrobacterium tumefaciens*-mediated gene transfer is the method of choice for generating transgenic dicots (for a review, see Hooykas and Schilperoort, 1992, Plant Mol. Biol. 19: 15-38) and can also be used for transforming monocots, although other transformation methods are often used for these plants. Presently, the method of choice for generating transgenic monocots is particle bombardment (microscopic gold or tungsten particles coated with the transforming DNA) of embryonic calli or developing embryos (Christou, 1992, Plant J. 2: 275-281; Shimamoto, 1994, Curr. Opin. Biotechnol. 5: 158-162; Vasil et al., 1992, Bio/Technology 10: 667-674). An alternative method for transformation of monocots is based on protoplast transformation as described by Omirulleh et al., 1993, Plant Mol. Biol. 21: 415-428. Additional transformation methods for use in accordance with the present disclosure include those described in U.S. Patent Nos. 6,395,966 and 7,151,204 (both of which are herein incorporated by reference in their entirety).

**[0083]** Following transformation, the transformants having incorporated the expression construct are selected and regenerated into whole plants according to methods well known in the art. Often the transformation procedure is designed for the selective elimination of selection genes either during regeneration or in the following generations by using, for example, co-transformation with two separate T-DNA constructs or site specific excision of the selection gene by a specific recombinase.

**[0084]** In addition to direct transformation of a particular plant genotype with a construct prepared according to the present invention, transgenic plants may be made by crossing a plant having the construct to a second plant lacking the construct. For example, a construct encoding a variant can be introduced into a particular plant variety by crossing, without the need for ever directly transforming a plant of that given variety. Therefore, the present invention encompasses not only a plant directly regenerated from cells which have been transformed in accordance with the present invention, but also the progeny of such plants. As used herein, progeny may refer to the offspring of any generation of a parent plant prepared in accordance with the present invention. Such progeny may include a DNA construct prepared in accordance with the present invention, or a portion of a DNA construct prepared in accordance with the present invention. Crossing results in the introduction of a transgene into a plant line by cross pollinating a starting line with a donor plant line. Non-limiting examples of such steps are further articulated in U.S. Patent No. 7,151,204.

**[0085]** Plants may be generated through a process of backcross conversion. For example, plants include plants referred to as a backcross converted genotype, line, inbred, or hybrid.

**[0086]** Genetic markers may be used to assist in the introgression of one or more transgenes of the invention from one genetic background into another. Marker assisted selection offers advantages relative to conventional breeding in that it can be used to avoid errors caused by phenotypic variations. Further, genetic markers may provide data regarding the relative degree of elite germplasm in the individual progeny of a particular cross. For example, when a plant with a desired trait which otherwise has a non-agronomically desirable genetic background is crossed to an elite parent, genetic markers may be used to select progeny which not only possess the trait of interest, but also have a relatively large proportion of the desired germplasm. In this way, the number of generations required to introgress one or more traits into a particular genetic background is minimized.

**[0087]** The present invention also relates to methods of producing a variant of the present invention

comprising: (a) cultivating a transgenic plant or a plant cell comprising a polynucleotide encoding the variant under conditions conducive for production of the variant; and (b) recovering the variant.

**Methods and Uses**

**[0088]** The present invention is also directed to methods for using the polypeptides having antimicrobial activity. The antimicrobial polypeptides are typically useful at any locus subject to contamination by microorganisms. Typically, loci are in aqueous systems such as cooling water systems, where microorganisms need to be killed or where their growth needs to be controlled. However, the present invention may also be used in all applications for which known antimicrobial compositions are useful, such as protection of wood, latex, adhesive, glue, paper, cardboard, textile, leather and feed.

**[0089]** Other uses include preservation of foods, beverages, cosmetics such as lotions, creams, gels, ointments, soaps, shampoos, conditioners, antiperspirants, deodorants, mouth wash, contact lens products or food ingredients.

**[0090]** In general it is contemplated that the antimicrobial polypeptides of the present invention are useful for cleaning, disinfecting or inhibiting microbial growth on any surface. Examples of surfaces, which may advantageously be contacted with the antimicrobial polypeptides of the invention, are surfaces of process equipment used e.g. dairies, chemical or pharmaceutical process plants. The antimicrobial polypeptides of the invention should be used in an amount, which is effective for cleaning, disinfecting or inhibiting microbial growth on the surface in question.

**[0091]** The antimicrobial polypeptides of the invention may additionally be used for cleaning surfaces and cooking utensils in food processing plants and in any area in which food is prepared or served such as hospitals, nursing homes and restaurants.

**[0092]** The invention also relates to the use of an antimicrobial polypeptide or composition of the invention as a medicament. Further, an antimicrobial polypeptide or composition of the invention may also be used for the manufacture of a medicament for controlling or combating microorganisms, such as fungal organisms or bacteria, preferably gram negative bacteria.

**[0093]** The composition and antimicrobial polypeptide of the invention may be used as an antimicrobial veterinarian or human therapeutic or prophylactic agent. Thus, the composition and antimicrobial polypeptide of the invention may be used in the preparation of veterinarian or human therapeutic agents or prophylactic agents for the treatment of microbial infections, such as bacterial or fungal infections, preferably gram positive bacterial infections. In particular the microbial infections may be associated with lung diseases including, but not limited to, tuberculosis, pneumonia and cystic fibrosis; skin infections and infections in the eye or the mouth; and sexually transmitted diseases including, but not limited to, gonorrhea and chlamydia. The invention also relates to wound healing compositions or products such as bandages, medical devices such as, e.g., catheters.

**[0094]** The composition of the invention comprises an effective amount of the antimicrobial polypeptide of the invention.

**[0095]** The term "effective amount" when used herein is intended to mean an amount of the antimicrobial polypeptides of the invention, which is sufficient to inhibit growth of the microorganisms in question.

**[0096]** Formulations of the antimicrobial polypeptides of the invention are administered to a host suffering from or predisposed to a microbial infection. Administration may be topical, localized or systemic, depending on the specific microorganism, preferably it will be localized. Generally the dose of the antimicrobial polypeptides of the invention will be sufficient to decrease the microbial population by at least about 50%, usually by at least 1 log, and may be by 2 or more logs of killing. The compounds of the present invention are administered at a dosage that reduces the microbial population while minimizing any side-effects. It is contemplated that the composition will be obtained and used under the guidance of a physician for *in vivo* use. The antimicrobial polypeptides of the invention are particularly useful for killing gram negative bacteria, including *Pseudomonas aeruginosa,* and *Chlamydia trachomatis;* and gram-positive bacteria, including streptococci such as *Streptococcus pneumonia, S. uberis, S. hyointestinalis, S. pyogenes* and *S. agalactiae;* and staphylococci such as *Staphylococcus aureus, S. epidermidis, S. simulans, S. xylosus* and *S. carnosus.*

**[0097]** Formulations of the antimicrobial polypeptides of the invention may be administered to a host suffering from or predisposed to a microbial lung infection, such as pneumonia; or to a microbial wound infection, such as a bacterial wound infection.

**[0098]** Formulations of the antimicrobial polypeptides of the invention may also be administered to a host suffering from or predisposed to a skin infection, such as acne, atopic dermatitis or seborrheic dermatitis; preferably the skin infection is a bacterial skin infection, e.g. caused by *Staphylococcus epidermidis, Staphylococcus aureus, Propionibacterium acnes, Pityrosporum ovale* or *Malassezia furfur.*

**[0099]** The antimicrobial polypeptides of the invention are also useful for *in vitro* formulations to kill microbes, particularly where one does not wish to introduce quantities of conventional antibiotics. For example, the antimicrobial polypeptides of the invention may be added to animal and/or human food preparations; or they may be included as an additive for *in vitro* cultures of cells, to prevent the overgrowth of microbes in tissue culture.

**[0100]** The susceptibility of a particular microbe to killing with the antimicrobial polypeptides of the invention may be determined by *in vitro* testing, as detailed in the experimental section. Typically a culture of the microbe is combined with the antimicrobial polypeptide at varying concentrations for a period of time sufficient to allow the protein to act, usually between about one hour and one day. The viable microbes are then counted, and the level of killing determined.

**[0101]** Microbes of interest include, but are not limited to, Gram-negative bacteria, for example: *Citrobacter sp.; Enterobacter sp.; Escherichia sp., e.g. E. coli; Klebsiella sp.; Morganella sp.; Proteus sp.; Providencia sp.; Salmonella sp., e.g. S. typhi, S. typhimurium; Serratia sp.; Shigella sp.; Pseudomonas sp., e.g. P. aeruginosa; Yersinia sp., e.g. Y. pestis, Y. pseudotuberculosis, Y. enterocolitica; Franciscella sp.; Pasturella sp.; Vibrio sp., e.g. V. cholerae, V. parahemolyticus; Campylobacter sp., e.g. C. jejuni; Haemophilus sp., e.g. H. influenzae, H. ducreyi; Bordetella sp., e.g. B. pertussis, B. bronchiseptica, B. parapertussis; Brucella sp., Neisseria sp., e.g. N. gonorrhoeae, N. meningitidis, etc.* Other bacteria of interest include *Legionella sp., e.g. L. pneumophila; Listeria sp., e.g. L. monocytogenes; Mycoplasma sp., e.g. M. hominis, M. pneumoniae; Mycobacterium sp., e.g. M. tuberculosis, M. leprae; Treponema sp., e.g. T. pallidum; Borrelia sp., e.g. B. burgdorferi; Leptospirae sp.; Rickettsia sp., e.g. R. rickettsii, R. typhi; Chlamydia sp., e.g. C. trachomatis, C. pneumoniae, C. psittaci; Helicobacter sp., e.g. H. pylori, etc.*

**[0102]** Non-bacterial pathogens of interest include fungal and protozoan pathogens, *e.g. Plasmodia sp., e.g. P. falciparum, Trypanosoma sp., e.g. T. brucei;* shistosomes; *Entaemoeba sp., Cryptococcus sp., Candida sp., e.g. C. albicans; etc.*

**[0103]** Various methods for administration may be employed. The polypeptide formulation may be given orally, or may be injected intravascularly, subcutaneously, peritoneally, by aerosol, opthalmically, intra-bladder, topically, *etc.* For example, methods of administration by inhalation are well-known in the art. The dosage of the therapeutic formulation will vary widely, depending on the specific antimicrobial polypeptide to be administered, the nature of the disease, the frequency of administration, the manner of administration, the clearance of the agent from the host, and the like. The initial dose may be larger, followed by smaller maintenance doses. The dose may be administered as infrequently as weekly or biweekly, or fractionated into smaller doses and administered once or several times daily, semi-weekly, *etc.* to maintain an effective dosage level. In many cases, oral administration will require a higher dose than if administered intravenously. The amide bonds, as well as the amino and carboxy termini, may be modified for greater stability on oral administration. For example, the carboxy terminus may be amidated.

**Formulations**

**[0104]** The compounds of this invention can be incorporated into a variety of formulations for therapeutic administration. More particularly, the compounds of the present invention can be formulated into pharmaceutical compositions by combination with appropriate, pharmaceutically acceptable carriers or diluents, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, creams, foams, solutions, suppositories, injections, inhalants, gels, microspheres, lotions, and aerosols. As such, administration of the compounds can be achieved in various ways, including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, transdermal, intracheal, *etc.,* administration. The antimicrobial polypeptides of the invention may be systemic after administration or may be localized by the use of an implant or other formulation that acts to retain the active dose at the site of implantation.

**[0105]** The compounds of the present invention can be administered alone, in combination with each other, or they can be used in combination with other known compounds *(e.g.,* perforin, anti-inflammatory agents, antibiotics, *etc.)* In pharmaceutical dosage forms, the compounds may be administered in the form of their pharmaceutically acceptable salts. The following methods and excipients are merely exemplary and are in no way limiting.

**[0106]** For oral preparations, the compounds can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, for example, with conventional additives, such as lactose, mannitol, corn starch or potato starch; with binders, such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators, such as corn starch, potato starch or sodium carboxymethylcellulose; with lubricants, such as talc or magnesium stearate; and if desired, with diluents, buffering agents, moistening agents, preservatives and flavoring agents.

**[0107]** The compounds can be formulated into preparations for injections by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

**[0108]** The compounds can be utilized in aerosol formulation to be administered via inhalation. The compounds of the present invention can be formulated into pressurized acceptable propellants such as dichlorodifluoromethane, propane, nitrogen and the like.

**[0109]** Furthermore, the compounds can be made into suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. The compounds of the present invention can be administered rectally via a suppository. The suppository can include vehicles such as cocoa butter, carbowaxes and polyethylene glycols, which melt at body temperature, yet are solidified at room temperature.

**[0110]** Unit dosage forms for oral or rectal administration such as syrups, elixirs, and suspensions may be provided wherein each dosage unit, for example, teaspoonful, tablespoonful, tablet or suppository, contains a predetermined amount of the composition containing one or more compounds of the present invention. Similarly, unit dosage forms for injection or intravenous administration may comprise the compound of the present invention in a composition as a solution in sterile water, normal saline or another pharmaceutically acceptable carrier.

**[0111]** Implants for sustained release formulations are well-known in the art. Implants are formulated as microspheres, slabs, *etc.* with biodegradable or non-biodegradable polymers. For example, polymers of lactic acid and/or glycolic acid form an erodible polymer that is well-tolerated by the host. The implant containing the antimicrobial polypeptides of the invention is placed in proximity to the site of infection, so that the local concentration of active agent is increased relative to the rest of the body.

**[0112]** The term "unit dosage form", as used herein, refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of compounds of the present invention calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier or vehicle. The specifications for the unit dosage forms of the present invention depend on the particular compound employed and the effect to be achieved, and the pharmacodynamics associated with the compound in the host.

**[0113]** The pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents, are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are readily available to the public.

**[0114]** Typical dosages for systemic administration range from 0.1 pg to 100 milligrams per kg weight of subject per administration. A typical dosage may be one tablet taken from two to six times daily, or one time-release capsule or tablet taken once a day and containing a proportionally higher content of active ingredient. The time-release effect may be obtained by capsule materials that dissolve at different pH values, by capsules that release slowly by osmotic pressure, or by any other known means of controlled release.

**[0115]** Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Some of the specific compounds are more potent than others. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means. A preferred means is to measure the physiological potency of a given compound.

**[0116]** The use of liposomes as a delivery vehicle is one method of interest. The liposomes fuse with the cells of the target site and deliver the contents of the lumen intracellularly. The liposomes are maintained in contact with the cells for sufficient time for fusion, using various means to maintain contact, such as isolation, binding agents, and the like. In one aspect of the invention, liposomes are designed to be aerosolized for pulmonary administration. Liposomes may be prepared with purified proteins or peptides that mediate fusion of membranes, such as Sendai virus or influenza virus, etc. The lipids may be any

useful combination of known liposome forming lipids, including cationic or zwitterionic lipids, such as phosphatidylcholine. The remaining lipid will be normally be neutral or acidic lipids, such as cholesterol, phosphatidyl serine, phosphatidyl glycerol, and the like.

**[0117]** For preparing the liposomes, the procedure described by Kato et al. (1991) J. Biol. Chem. 266:3361 may be used. Briefly, the lipids and lumen composition containing peptides are combined in an appropriate aqueous medium, conveniently a saline medium where the total solids will be in the range of about 1-10 weight percent. After intense agitation for short periods of time, from about 5-60 sec., the tube is placed in a warm water bath, from about 25-40°C and this cycle repeated from about 5-10 times. The composition is then sonicated for a convenient period of time, generally from about 1-10 sec. and may be further agitated by vortexing. The volume is then expanded by adding aqueous medium, generally increasing the volume by about from 1-2 fold, followed by shaking and cooling. This method allows for the incorporation into the lumen of high molecular weight molecules.

**Formulations with Other Active Agents**

**[0118]** For use in the subject methods, the antimicrobial polypeptides of the invention may be formulated with other pharmaceutically active agents, particularly other antimicrobial agents. Other agents of interest include a wide variety of antibiotics, as known in the art. Classes of antibiotics include penicillins, e.g. penicillin G, penicillin V, methicillin, oxacillin, carbenicillin, nafcillin, ampicillin, etc.; penicillins in combination with beta-lactamase inhibitors, cephalosporins, e.g. cefaclor, cefazolin, cefuroxime, moxalactam, etc.; carbapenems; monobactams; aminoglycosides; tetracyclines; macrolides; lincomycins; polymyxins; sulfonamides; quinolones; cloramphenical; metronidazole; spectinomycin; trimethoprim; vancomycin; etc.

**[0119]** Anti-mycotic agents are also useful, including polyenes, e.g. amphotericin B, nystatin; 5-flucosyn; and azoles, e.g. miconazol, ketoconazol, itraconazol and fluconazol. Antituberculotic drugs include isoniazid, ethambutol, streptomycin and rifampin. Cytokines may also be included in a formulation of the antimicrobial polypeptides of the invention, e.g. interferon gamma, tumor necrosis factor alpha, interleukin 12, etc.

**[0120]** The present invention is further described by the following examples that should not be construed as limiting the scope of the invention.

**EXAMPLES**

**[0121]** NZ17074 is the antimicrobial peptide of SEQ ID NO: 70.

**[0122]** All examples referring to peptides of SEQ ID NOs: 1 to 71, 73 to 349 and 351 to 548 are for reference only.

**EXAMPLE 1**

**Isolation of variants of SEQ ID NO: 2 having improved antimicrobial activity**

**[0123]** The cDNA encoding SEQ ID NO: 2 was fused to the proregion of plectasin (see Mygind et al; Nature, 437, 2005) and the Mating Factor alpha-leader from *Saccharomyces cerevisiae* and introduced into the inducible *S. cerevisiae* expression vector, pYES2, and transformed into *S. cerevisiae.* This system takes advantage of the GAL1 promoter which is repressed by glucose and activated by galactose.

**[0124]** Several strategies were used for variant generation of the polynucleotide of SEQ ID NO:1. The resulting libraries were cloned and expressed in *S. cerevisiae.* Transformed clones were screened on a plate assay containing growth media supplemented with 1.5% galactose and 0.5% glucose and either horse blood (2.5 - 5%) or serum (5%), overlayed with the target organism, *E.coli* ATCC 10536 (See Raventos et al Comb Chem High Throughput Screen. 2005; 8:219-33).

**[0125]** The plate assay conditions fully inhibited the activity of the antimicrobial peptide of SEQ ID NO: 2 (the parent antimicrobial peptide). Variants exhibiting improved antimicrobial activity (giving rise to clearing zones) in the presence of 2.5% blood, 5% blood or 5% serum were picked and sequenced, and are shown in Table 1.

**Plate assay screening procedure**

**[0126]** Approximately, 300 *Saccharomyces cerevisiae* colonies expressing arenicin variants were spread on screening plates containing either horse blood (2.5% or 5%) or 5% horse serum (see composition of the plates below). Plates were incubated 3 hours at 30 degrees Celsius to allow them to dry. Next, 25 ml overlay temperated at 42 degrees Celsius was added to the plates. After the media had solidified, the plates were incubated 3 days at 30 degrees Celsius.

**[0127]** On day 4, plates were overlayed with pre-warmed media at 42 degrees Celsius containing either 2.5% or 5% horse blood or 5% horse serum and the target bacteria, *E. coli* ATCC 10536 (see below for details on media composition). After the overlay solidified, plates were incubated 16 hours at 37 degrees Celsius. Next day, plates were colored by adding 10 ml of 1.5 mM MTT to the plates and incubated at room temperature for 30 minutes. Clones giving rise to clearing zones were picked and sequenced.

**Plate and media composition**

**[0128]** Three different types of screening plates a), b) and c) were used in the screening:

**a) Plates + 2.5% horse blood**

**[0129]** The bottom layer contains 50 ml of 1.5% agarose + ¼ SC media + 2.5% blood + 1.5% galactose + 0.5% glucose. The first overlay contains 25 ml of 1% agarose + ¼ SC media + 2.5% blood + 1.5% galactose + 0.5% glucose. The top overlay contains 25 ml 0.2% MHB (#212322; BD) + 1% agarose (Sigma A-4718) + 2.5% horse blood and $1.25x10^6$ colony forming units (cfu) of *E.coli* ATCC 10536.

**b) Plates + 5% horse blood**

**[0130]** The bottom layer contains 50 ml of 1.5% agarose + ¼ SC media + 5% blood + 1.5% galactose +

0.5% glucose. The first overlay contains 25 ml of 1% agarose + ¼ SC media + 5% blood + 1.5% galactose + 0.5% glucose. The top overlay contains 25 ml 0.2% MHB (#212322; BD) + 1% agarose (Sigma A-4718) + 5% horse blood and $1.25x10^6$ colony forming units (cfu) of *E.coli* ATCC 10536.

**c) Plates + 5% horse serum**

**[0131]** The bottom layer contains 50 ml of 1.5% agarose + ½ SC media + 5% serum + 1.5% galactose + 0.5% glucose. The first overlay contains 25 ml of 1% agarose + ½ SC media + 5% serum + 1.5% galactose + 0.5% glucose. The top overlay contains 25 ml 0.2% MHB (#212322; BD) + 1% agarose (Sigma A-4718) + 5% horse serum and $1.25x10^6$ colony forming units (cfu) of *E.coli* ATCC 10536.

**Composition of SC media (450 ml)**

**[0132]**

| | |
|---|---|
| Yeast Nitrogen Base w/o amino acids: | 3.75 g |
| Succinic acid: | 5.65 g |
| Sodium hydroxide: | 3.4 g |
| Casamino acid vitamin assay: | 2.8 g |
| L-Tryptophan: | 0.05 g |
| Water: | 450 ml |

pH was adjusted to 6 and the media was autoclaved and diluted ¼ when preparing the blood plates and ½ when preparing the serum plates.

**MTT: (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide, Sigma 13,503-8)**

**Determination of the protein binding**

**[0133]** Protein binding assays were performed as follows. The purified peptides were mixed with 90% serum and centrifuged through a 30 kDa filter. The ultra-filtrate and the non filtrated serum samples were quantified by HPLC measurements and the protein binding was subsequently calculated.

**[0134]** The antimicrobial peptide of SEQ ID NO: 2 (the parent antimicrobial peptide) exhibited a protein binding of 99.5% in this assay. As shown in Table 1, all exemplified variants exhibit a lower protein binding than the antimicrobial peptide of SEQ ID NO: 2.

Table 1. Variants exhibiting improved antimicrobial activity and reduced protein binding. The symbol "-" means "not analyzed".

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 3 | F2A | GACWYVCVYRNGVRVCYRRCN | 86 |
| 4 | W4A | GFCAYVCVYRNGVRVCYRRCN | 89 |
| 5 | W4E | GFCEYVCVYRNGVRVCYRRCN | - |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 6 | W4G | GFCGYVCVYRNGVRVCYRRCN | - |
| 7 | W4S | GFCSYVCVYRNGVRVCYRRCN | 68 |
| 8 | W4T | GFCTYVCVYRNGVRVCYRRCN | - |
| 9 | W4Y | GFCYYVCVYRNGVRVCYRRCN | - |
| 10 | Y5K | GFCWKVCVYRNGVRVCYRRCN | 64 |
| 11 | Y5N | GFCWNVCVYRNGVRVCYRRCN | 73 |
| 12 | Y5R | GFCWRVCVYRNGVRVCYRRCN | - |
| 13 | V6A | GFCWYACVYRNGVRVCYRRCN | - |
| 14 | V6E | GFCWYECVYRNGVRVCYRRCN | - |
| 15 | V6G | GFCWYGCVYRNGVRVCYRRCN | 96 |
| 16 | V6L | GFCWYLCVYRNGVRVCYRRCN | - |
| 17 | V6N | GFCWYNCVYRNGVRVCYRRCN | - |
| 18 | V6R | GFCWYRCVYRNGVRVCYRRCN | - |
| 19 | V6S | GFCWYSCVYRNGVRVCYRRCN | 89 |
| 20 | V6W | GFCWYWCVYRNGVRVCYRRCN | 99 |
| 21 | V8A | GFCWYVCAYRNGVRVCYRRCN | 98.5 |
| 22 | V8G | GFCWYVCGYRNGVRVCYRRCN | - |
| 23 | V8H | GFCWYVCHYRNGVRVCYRRCN | 98 |
| 24 | V8S | GFCWYVCSYRNGVRVCYRRCN | 85 |
| 25 | V8Y | GFCWYVCYYRNGVRVCYRRCN | 98 |
| 26 | Y9I | GFCWYVCVIRNGVRVCYRRCN | - |
| 27 | Y9K | GFCWYVCVKRNGVRVCYRRCN | - |
| 28 | Y9R | GFCWYVCVRRNGVRVCYRRCN | 92 |
| 29 | V13A | GFCWYVCVYRNGARVCYRRCN | 99 |
| 30 | V13G | GFCWYVCVYRNGGRVCYRRCN | 99 |
| 31 | V13K | GFCWYVCVYRNGKRVCYRRCN | - |
| 32 | V13L | GFCWYVCVYRNGLRVCYRRCN | - |
| 33 | V13P | GFCWYVCVYRNGPRVCYRRCN | 99 |
| 34 | V13Q | GFCWYVCVYRNGQRVCYRRCN | - |
| 35 | V13R | GFCWYVCVYRNGRRVCYRRCN | - |
| 36 | V13S | GFCWYVCVYRNGSRVCYRRCN | 60 |
| 37 | V15A | GFCWYVCVYRNGVRACYRRCN | - |
| 38 | V15G | GFCWYVCVYRNGVRGCYRRCN | 93 |
| 39 | V15H | GFCWYVCVYRNGVRHCYRRCN | 98 |
| 40 | V15K | GFCWYVCVYRNGVRKCYRRCN | - |
| 41 | V15N | GFCWYVCVYRNGVRNCYRRCN | 97 |
| 42 | V15Q | GFCWYVCVYRNGVRQCYRRCN | 96 |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 43 | V15R | GFCWYVCVYRNGVRRCYRRCN | - |
| 44 | V15S | GFCWYVCVYRNGVRSCYRRCN | 85 |
| 45 | V15T | GFCWYVCVYRNGVRTCYRRCN | 98 |
| 46 | Y17H | GFCWYVCVYRNGVRVCHRRCN | 88 |
| 47 | Y17K | GFCWYVCVYRNGVRVCKRRCN | 89 |
| 48 | Y17N | GFCWYVCVYRNGVRVCNRRCN | 68 |
| 49 | Y17R | GFCWYVCVYRNGVRVCRRRCN | - |
| 50 | N21H | GFCWYVCVYRNGVRVCYRRCH | - |
| 51 | N21K | GFCWYVCVYRNGVRVCYRRCK | - |
| 52 | N21R | GFCWYVCVYRNGVRVCYRRCR | - |
| 53 | N21S | GFCWYVCVYRNGVRVCYRRCS | 99 |
| 54 | N21T | GFCWYVCVYRNGVRVCYRRCT | 99 |
| 55 | G1R+N21R | RFCWYVCVYRNGVRVCYRRCR | - |
| 56 | W4F+Y17R | GFCFYVCVYRNGVRVCRRRCN | 94 |
| 57 | W4A+Y5H | GFCAHVCVYRNGVRVCYRRCN | - |
| 58 | W4A+Y5R | GFCARVCVYRNGVRVCYRRCN | - |
| 59 | W4F+Y9R | GFCFYVCVRRNGVRVCYRRCN | - |
| 60 | W4G+Y5H | GFCGHVCVYRNGVRVCYRRCN | 64 |
| 61 | W4G+Y5R | GFCGRVCVYRNGVRVCYRRCN | 72 |
| 62 | W4S+V15A | GFCSYVCVYRNGVRACYRRCN | - |
| 63 | W4S+Y5R | GFCSRVCVYRNGVRVCYRRCN | - |
| 64 | W4Y+Y5R | GFCYRVCVYRNGVRVCYRRCN | - |
| 65 | Y5F+V15Q | GFCWFVCVYRNGVRQCYRRCN | - |
| 66 | Y5H+V15S | GFCWHVCVYRNGVRSCYRRCN | - |
| 67 | Y5H+Y17R | GFCWHVCVYRNGVRVCRRRCN | - |
| 68 | Y5K+Y17S | GFCWKVCVYRNGVRVCSRRCN | 87 |
| 69 | Y5N+V15S | GFCWNVCVYRNGVRSCYRRCN | - |
| 70 | Y5N+Y17H | GFCWNVCVYRNGVRVCHRRCN | 79 |
| 71 | Y5R+V15P | GFCWRVCVYRNGVRPCYRRCN | - |
| 72 | Y5R+V6A | GFCWRACVYRNGVRVCYRRCN | 97 |
| 73 | Y5R+V8G | GFCWRVCGYRNGVRVCYRRCN | - |
| 74 | Y5R+V8H | GFCWRVCHYRNGVRVCYRRCN | 99 |
| 75 | Y5R+V8S | GFCWRVCSYRNGVRVCYRRCN | - |
| 76 | Y5R+Y17H | GFCWRVCVYRNGVRVCHRRCN | 92 |
| 77 | Y5R+Y17N | GFCWRVCVYRNGVRVCNRRCN | - |
| 78 | Y5S+V15S | GFCWSVCVYRNGVRSCYRRCN | - |
| 79 | V6A+V13A | GFCWYACVYRNGARVCYRRCN | - |
| 80 | V6A+V13K | GFCWYACVYRNGKRVCYRRCN | 96 |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 81 | V6A+V15A | GFCWYACVYRNGVRACYRRCN | - |
| 82 | V6A+Y17H | GFCWYACVYRNGVRVCHRRCN | - |
| 83 | V6M+V8G | GFCWYMCGYRNGVRVCYRRCN | - |
| 84 | V8A+V15A | GFCWYVCAYRNGVRACYRRCN | - |
| 85 | V8S+V13K | GFCWYVCSYRNGKRVCYRRCN | - |
| 86 | Y9K+V13A | GFCWYVCVKRNGARVCYRRCN | - |
| 87 | Y9K+V15S | GFCWYVCVKRNGVRSCYRRCN | 93 |
| 88 | R10K+V15S | GFCWYVCVYKNGVRSCYRRCN | - |
| 89 | R10K+Y17H | GFCWYVCVYKNGVRVCHRRCN | 90 |
| 90 | R10P+V13G | GFCWYVCVYPNGGRVCYRRCN | - |
| 91 | N11R+V15Q | GFCWYVCVYRRGVRQCYRRCN | - |
| 92 | V13A+Y17C | GFCWYVCVYRNGARVCCRRCN | - |
| 93 | V13G+V15K | GFCWYVCVYRNGGRKCYRRCN | - |
| 94 | V15L+Y17H | GFCWYVCVYRNGVRLCHRRCN | - |
| 95 | G1A+Y5N+Y17H | AFCWNVCVYRNGVRVCHRRCN | - |
| 96 | G1D+Y5N+Y17H | DFCWNVCVYRNGVRVCHRRCN | - |
| 97 | G1F+Y5N+Y17H | FFCWNVCVYRNGVRVCHRRCN | - |
| 98 | G1H+Y5N+Y17H | HFCWNVCVYRNGVRVCHRRCN | 77 |
| 99 | G1I+Y5N+Y17H | IFCWNVCVYRNGVRVCHRRCN | - |
| 100 | G1K+Y5N+Y17H | KFCWNVCVYRNGVRVCHRRCN | 78 |
| 101 | G1M+Y5N+Y17H | MFCWNVCVYRNGVRVCHRRCN | 81 |
| 102 | G1Q+Y5N+Y17H | QFCWNVCVYRNGVRVCHRRCN | - |
| 103 | G1R+Y5N+Y17H | RFCWNVCVYRNGVRVCHRRCN | - |
| 104 | G1S+Y5N+Y17H | SFCWNVCVYRNGVRVCHRRCN | - |
| 105 | G1T+Y5N+Y17H | TFCWNVCVYRNGVRVCHRRCN | - |
| 106 | G1V+Y5N+Y17H | VFCWNVCVYRNGVRVCHRRCN | - |
| 107 | G1W+Y5N+Y17H | WFCWNVCVYRNGVRVCHRRCN | - |
| 108 | G1Y+Y5N+Y17H | YFCWNVCVYRNGVRVCHRRCN | - |
| 109 | F2G+Y5N+Y17H | GGCWNVCVYRNGVRVCHRRCN | - |
| 110 | F2H+Y5N+Y17H | GHCWNVCVYRNGVRVCHRRCN | - |
| 111 | F2I+Y5N+Y17H | GICWNVCVYRNGVRVCHRRCN | - |
| 112 | F2L+Y5N+Y17H | GLCWNVCVYRNGVRVCHRRCN | - |
| 113 | F2M+Y5N+Y17H | GMCWNVCVYRNGVRVCHRRCN | - |
| 114 | F2P+Y5N+Y17H | GPCWNVCVYRNGVRVCHRRCN | - |
| 115 | F2V+Y5N+Y17H | GVCWNVCVYRNGVRVCHRRCN | - |
| 116 | F2W+Y5N+Y17H | GWCWNVCVYRNGVRVCHRRCN | - |
| 117 | F2Y+Y5N+Y17H | GYCWNVCVYRNGVRVCHRRCN | - |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 118 | C3L+W4Q+Y17H | GFLQYVCVYRNGVRVCHRRCN | - |
| 119 | W4A+V6A+Y9K | GFCAYACVKRNGVRVCYRRCN | - |
| 120 | W4A+Y5K+V15S | GFCAKVCVYRNGVRSCYRRCN | 69 |
| 121 | W4A+Y5R+V15A | GFCARVCVYRNGVRACYRRCN | - |
| 122 | W4A+Y5R+V15S | GFCARVCVYRNGVRSCYRRCN | 81 |
| 123 | W4A+Y5R+V15T | GFCARVCVYRNGVRTCYRRCN | - |
| 124 | W4A+Y5R+V8S | GFCARVCSYRNGVRVCYRRCN | - |
| 125 | W4A+Y5R+Y9K | GFCARVCVKRNGVRVCYRRCN | 90 |
| 126 | W4A+Y5W+V15Q | GFCAWVCVYRNGVRQCYRRCN | - |
| 127 | W4A+Y9R+V15S | GFCAYVCVRRNGVRSCYRRCN | - |
| 128 | W4F+V8A+V15S | GFCFYVCAYRNGVRSCYRRCN | - |
| 129 | W4F+Y5H+V15S | GFCFHVCVYRNGVRSCYRRCN | - |
| 130 | W4F+Y5N+V15S | GFCFNVCVYRNGVRSCYRRCN | - |
| 131 | W4F+Y5N+Y17H | GFCFNVCVYRNGVRVCHRRCN | - |
| 132 | W4F+Y5R+V15K | GFCFRVCVYRNGVRKCYRRCN | - |
| 133 | W4F+Y5R+V15Q | GFCFRVCVYRNGVRQCYRRCN | - |
| 134 | W4F+Y5R+V15S | GFCFRVCVYRNGVRSCYRRCN | - |
| 135 | W4F+Y5R+Y17H | GFCFRVCVYRNGVRVCHRRCN | - |
| 136 | W4F+Y5R+Y17Q | GFCFRVCVYRNGVRVCQRRCN | - |
| 137 | W4F+Y9K+Y17H | GFCFYVCVKRNGVRVCHRRCN | 86 |
| 138 | W4G+Y5H+N21A | GFCGHVCVYRNGVRVCYRRCA | - |
| 139 | W4G+Y5H+N21K | GFCGHVCVYRNGVRVCYRRCK | - |
| 140 | W4G+Y5H+N21L | GFCGHVCVYRNGVRVCYRRCL | - |
| 141 | W4G+Y5H+N21M | GFCGHVCVYRNGVRVCYRRCM | - |
| 142 | W4G+Y5H+N21P | GFCGHVCVYRNGVRVCYRRCP | - |
| 143 | W4G+Y5H+N21R | GFCGHVCVYRNGVRVCYRRCR | - |
| 144 | W4G+Y5H+N21S | GFCGHVCVYRNGVRVCYRRCS | 68 |
| 145 | W4G+Y5H+N21Y | GFCGHVCVYRNGVRVCYRRCY | - |
| 146 | W4G+Y5H+V15A | GFCGHVCVYRNGVRACYRRCN | - |
| 147 | W4G+Y5H+V15F | GFCGHVCVYRNGVRFCYRRCN | - |
| 148 | W4G+Y5H+V15G | GFCGHVCVYRNGVRGCYRRCN | - |
| 149 | W4G+Y5H+V15H | GFCGHVCVYRNGVRHCYRRCN | - |
| 150 | W4G+Y5H+V15I | GFCGHVCVYRNGVRICYRRCN | - |
| 151 | W4G+Y5H+V15L | GFCGHVCVYRNGVRLCYRRCN | - |
| 152 | W4G+Y5H+V15M | GFCGHVCVYRNGVRMCYRRCN | - |
| 153 | W4G+Y5H+V15N | GFCGHVCVYRNGVRNCYRRCN | - |
| 154 | W4G+Y5H+V15Q | GFCGHVCVYRNGVRQCYRRCN | - |
| 155 | W4G+Y5H+V15R | GFCGHVCVYRNGVRRCYRRCN | 83 |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 156 | W4G+Y5H+V15S | GFCGHVCVYRNGVRSCYRRCN | - |
| 157 | W4G+Y5H+V15T | GFCGHVCVYRNGVRTCYRRCN | - |
| 158 | W4G+Y5H+V15W | GFCGHVCVYRNGVRWCYRRCN | - |
| 159 | W4G+Y5H+V15Y | GFCGHVCVYRNGVRYCYRRCN | - |
| 160 | W4G+Y5H+Y17F | GFCGHVCVYRNGVRVCFRRCN | - |
| 161 | W4G+Y5H+Y17G | GFCGHVCVYRNGVRVCGRRCN | - |
| 162 | W4G+Y5H+Y17I | GFCGHVCVYRNGVRVCIRRCN | - |
| 163 | W4G+Y5H+Y17L | GFCGHVCVYRNGVRVCLRRCN | - |
| 164 | W4G+Y5H+Y17M | GFCGHVCVYRNGVRVCMRRCN | - |
| 165 | W4G+Y5H+Y17T | GFCGHVCVYRNGVRVCTRRCN | - |
| 166 | W4G+Y5H+Y17V | GFCGHVCVYRNGVRVCVRRCN | - |
| 167 | W4G+Y5H+Y17W | GFCGHVCVYRNGVRVCWRRCN | - |
| 168 | W4G+Y5K+V15H | GFCGKVCVYRNGVRHCYRRCN | - |
| 169 | W4G+Y5R+V15L | GFCGRVCVYRNGVRLCYRRCN | - |
| 170 | W4G+Y5R+V15R | GFCGRVCVYRNGVRRCYRRCN | 87 |
| 171 | W4G+Y5R+V15T | GFCGRVCVYRNGVRTCYRRCN | 84 |
| 172 | W4G+Y5R+Y9R | GFCGRVCVRRNGVRVCYRRCN | 88 |
| 173 | W4G+Y5S+V15A | GFCGSVCVYRNGVRACYRRCN | - |
| 174 | W4G+Y5S+V15K | GFCGSVCVYRNGVRKCYRRCN | - |
| 175 | W4G+Y5S+V15R | GFCGSVCVYRNGVRRCYRRCN | - |
| 176 | W4G+Y9R+V15S | GFCGYVCVRRNGVRSCYRRCN | - |
| 177 | W4I+Y5N+Y17H | GFCINVCVYRNGVRVCHRRCN | - |
| 178 | W4L+Y5H+V15Q | GFCLHVCVYRNGVRQCYRRCN | - |
| 179 | W4L+Y5K+V15K | GFCLKVCVYRNGVRKCYRRCN | - |
| 180 | W4L+Y5R+V15Q | GFCLRVCVYRNGVRQCYRRCN | - |
| 181 | W4L+Y5R+V15S | GFCLRVCVYRNGVRSCYRRCN | - |
| 182 | W4M+Y5E+Y17T | GFCMEVCVYRNGVRVCTRRCN | - |
| 183 | W4M+Y5H+V15S | GFCMHVCVYRNGVRSCYRRCN | - |
| 184 | W4M+Y5N+Y17H | GFCMNVCVYRNGVRVCHRRCN | - |
| 185 | W4M+Y5R+V15T | GFCMRVCVYRNGVRTCYRRCN | - |
| 186 | W4M+Y5S+V15Q | GFCMSVCVYRNGVRQCYRRCN | - |
| 187 | W4M+Y5S+V15R | GFCMSVCVYRNGVRRCYRRCN | - |
| 188 | W4N+Y5R+V15I | GFCNRVCVYRNGVRICYRRCN | - |
| 189 | W4S+Y5K+V15R | GFCSKVCVYRNGVRRCYRRCN | - |
| 190 | W4S+Y5R+V15I | GFCSRVCVYRNGVRICYRRCN | - |
| 191 | W4T+Y5N+V15A | GFCTNVCVYRNGVRACYRRCN | - |
| 192 | W4T+Y5R+V15R | GFCTRVCVYRNGVRRCYRRCN | - |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 193 | W4T+Y5R+V15T | GFCTRVCVYRNGVRTCYRRCN | - |
| 194 | W4T+Y5S+V15H | GFCTSVCVYRNGVRHCYRRCN | - |
| 195 | W4T+Y9K+V15K | GFCTYVCVKRNGVRKCYRRCN | 95 |
| 196 | W4V+Y5H+V15P | GFCVHVCVYRNGVRPCYRRCN | - |
| 197 | W4V+Y5H+Y17H | GFCVHVCVYRNGVRVCHRRCN | - |
| 198 | W4V+Y5K+V15Q | GFCVKVCVYRNGVRQCYRRCN | - |
| 199 | W4V+Y5N+Y17H | GFCVNVCVYRNGVRVCHRRCN | - |
| 200 | W4V+Y5R+V15G | GFCVRVCVYRNGVRGCYRRCN | - |
| 201 | W4V+Y5R+V15P | GFCVRVCVYRNGVRPCYRRCN | - |
| 202 | W4V+Y5R+V15Q | GFCVRVCVYRNGVRQCYRRCN | - |
| 203 | W4V+Y5R+V15R | GFCVRVCVYRNGVRRCYRRCN | - |
| 204 | W4V+Y5R+V15T | GFCVRVCVYRNGVRTCYRRCN | - |
| 205 | W4Y+Y5H+V15Y | GFCYHVCVYRNGVRYCYRRCN | - |
| 206 | W4Y+Y5K+V15S | GFCYKVCVYRNGVRSCYRRCN | 86 |
| 207 | W4Y+Y5N+V15R | GFCYNVCVYRNGVRRCYRRCN | 91 |
| 208 | W4Y+Y5N+Y17H | GFCYNVCVYRNGVRVCHRRCN | - |
| 209 | W4Y+Y5R+V15T | GFCYRVCVYRNGVRTCYRRCN | 89 |
| 210 | W4Y+Y5R+Y17H | GFCYRVCVYRNGVRVCHRRCN | 89 |
| 211 | W4Y+Y5R+Y17S | GFCYRVCVYRNGVRVCSRRCN | 96 |
| 212 | W4Y+Y5W+V15S | GFCYWVCVYRNGVRSCYRRCN | - |
| 213 | Y5H+V13A+V15S | GFCWHVCVYRNGARSCYRRCN | 95 |
| 214 | Y5H+V13S+V15S | GFCWHVCVYRNGSRSCYRRCN | - |
| 215 | Y5H+V15S+Y17S | GFCWHVCVYRNGVRSCSRRCN | - |
| 216 | Y5H+V8A+V13K | GFCWHVCAYRNGKRVCYRRCN | - |
| 217 | Y5H+V8A+V15S | GFCWHVCAYRNGVRSCYRRCN | - |
| 218 | Y5H+V8A+Y9R | GFCWHVCARRNGVRVCYRRCN | 99 |
| 219 | Y5H+V8H+G12S | GFCWHVCHYRNSVRVCYRRCN | 99 |
| 220 | Y5H+Y9S+V15K | GFCWHVCVSRNGVRKCYRRCN | - |
| 221 | Y5K+Y9S+Y17S | GFCWKVCVSRNGVRVCSRRCN | - |
| 222 | Y5N+G12A+Y17H | GFCWNVCVYRNAVRVCHRRCN | - |
| 223 | Y5N+G12D+Y17H | GFCWNVCVYRNDVRVCHRRCN | - |
| 224 | Y5N+G12E+Y17H | GFCWNVCVYRNEVRVCHRRCN | - |
| 225 | Y5N+G12F+Y17H | GFCWNVCVYRNFVRVCHRRCN | - |
| 226 | Y5N+G12H+Y17H | GFCWNVCVYRNHVRVCHRRCN | - |
| 227 | Y5N+G12K+Y17H | GFCWNVCVYRNKVRVCHRRCN | 80 |
| 228 | Y5N+G12R+Y17H | GFCWNVCVYRNRVRVCHRRCN | 86 |
| 229 | Y5N+G12Y+Y17H | GFCWNVCVYRNYVRVCHRRCN | 91 |
| 230 | Y5N+N11A+Y17H | GFCWNVCVYRAGVRVCHRRCN | 71 |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 231 | Y5N+N11G+Y17H | GFCWNVCVYRGGVRVCHRRCN | 66 |
| 232 | Y5N+N11H+Y17H | GFCWNVCVYRHGVRVCHRRCN | 85 |
| 233 | Y5N+N11Q+Y17H | GFCWNVCVYRQGVRVCHRRCN | 78 |
| 234 | Y5N+N11R+Y17H | GFCWNVCVYRRGVRVCHRRCN | 86 |
| 235 | Y5N+V13A+Y17H | GFCWNVCVYRNGARVCHRRCN | 64 |
| 236 | Y5N+V13F+Y17H | GFCWNVCVYRNGFRVCHRRCN | - |
| 237 | Y5N+V13H+Y17H | GFCWNVCVYRNGHRVCHRRCN | 40 |
| 238 | Y5N+V13Q+Y17H | GFCWNVCVYRNGQRVCHRRCN | - |
| 239 | Y5N+V13R+Y17H | GFCWNVCVYRNGRRVCHRRCN | 65 |
| 240 | Y5N+V13T+Y17H | GFCWNVCVYRNGTRVCHRRCN | - |
| 241 | Y5N+V13W+Y17H | GFCWNVCVYRNGWRVCHRRCN | - |
| 242 | Y5N+V13Y+Y17H | GFCWNVCVYRNGYRVCHRRCN | 83 |
| 243 | Y5N+V15A+Y17H | GFCWNVCVYRNGVRACHRRCN | - |
| 244 | Y5N+V15C+Y17H | GFCWNVCVYRNGVRCCHRRCN | - |
| 245 | Y5N+V15F+Y17H | GFCWNVCVYRNGVRFCHRRCN | 85 |
| 246 | Y5N+V15G+Y17H | GFCWNVCVYRNGVRGCHRRCN | 79 |
| 247 | Y5N+V15H+Y17H | GFCWNVCVYRNGVRHCHRRCN | - |
| 248 | Y5N+V15I+Y17H | GFCWNVCVYRNGVRICHRRCN | 58 |
| 249 | Y5N+V15L+Y17H | GFCWNVCVYRNGVRLCHRRCN | 83 |
| 250 | Y5N+V15M+Y17H | GFCWNVCVYRNGVRMCHRRCN | - |
| 251 | Y5N+V15N+Y17H | GFCWNVCVYRNGVRNCHRRCN | 71 |
| 252 | Y5N+V15R+Y17H | GFCWNVCVYRNGVRRCHRRCN | 76 |
| 253 | Y5N+V15W+Y17H | GFCWNVCVYRNGVRWCHRRCN | 94 |
| 254 | Y5N+V15Y+Y17H | GFCWNVCVYRNGVRYCHRRCN | 77 |
| 255 | Y5N+V6A+V15N | GFCWNACVYRNGVRNCYRRCN | - |
| 256 | Y5N+V6A+V15S | GFCWNACVYRNGVRSCYRRCN | - |
| 257 | Y5N+V6A+Y17H | GFCWNACVYRNGVRVCHRRCN | - |
| 258 | Y5N+V6A+Y9K | GFCWNACVKRNGVRVCYRRCN | 89 |
| 259 | Y5N+V6C+Y17H | GFCWNCCVYRNGVRVCHRRCN | - |
| 260 | Y5N+V6F+Y17H | GFCWNFCVYRNGVRVCHRRCN | 84 |
| 261 | Y5N+V6H+Y17H | GFCWNHCVYRNGVRVCHRRCN | - |
| 262 | Y5N+V6I+Y17H | GFCWNICVYRNGVRVCHRRCN | 88 |
| 263 | Y5N+V6L+Y17H | GFCWNLCVYRNGVRVCHRRCN | 80 |
| 264 | Y5N+V6M+Y17H | GFCWNMCVYRNGVRVCHRRCN | - |
| 265 | Y5N+V6Q+Y17H | GFCWNQCVYRNGVRVCHRRCN | - |
| 266 | Y5N+V6T+Y17H | GFCWNTCVYRNGVRVCHRRCN | - |
| 267 | Y5N+V6W+Y17H | GFCWNWCVYRNGVRVCHRRCN | 85 |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 268 | Y5N+V6Y+Y17H | GFCWNYCVYRNGVRVCHRRCN | - |
| 269 | Y5N+V8A+V13A | GFCWNVCAYRNGARVCYRRCN | - |
| 270 | Y5N+V8A+V15S | GFCWNVCAYRNGVRSCYRRCN | - |
| 271 | Y5N+V8A+Y17H | GFCWNVCAYRNGVRVCHRRCN | - |
| 272 | Y5N+V8F+Y17H | GFCWNVCFYRNGVRVCHRRCN | 74 |
| 273 | Y5N+V8G+Y17H | GFCWNVCGYRNGVRVCHRRCN | - |
| 274 | Y5N+V8I+Y17H | GFCWNVCIYRNGVRVCHRRCN | - |
| 275 | Y5N+V8L+Y17H | GFCWNVCLYRNGVRVCHRRCN | 80 |
| 276 | Y5N+V8W+Y17H | GFCWNVCWYRNGVRVCHRRCN | - |
| 277 | Y5N+V8Y+Y17H | GFCWNVCYYRNGVRVCHRRCN | - |
| 278 | Y5N+Y17H+N21A | GFCWNVCVYRNGVRVCHRRCA | - |
| 279 | Y5N+Y17H+N21C | GFCWNVCVYRNGVRVCHRRCC | - |
| 280 | Y5N+Y17H+N21F | GFCWNVCVYRNGVRVCHRRCF | - |
| 281 | Y5N+Y17H+N21G | GFCWNVCVYRNGVRVCHRRCG | 66 |
| 282 | Y5N+Y17H+N21H | GFCWNVCVYRNGVRVCHRRCH | 82 |
| 283 | Y5N+Y17H+N21I | GFCWNVCVYRNGVRVCHRRCI | - |
| 284 | Y5N+Y17H+N21K | GFCWNVCVYRNGVRVCHRRCK | 72 |
| 285 | Y5N+Y17H+N21L | GFCWNVCVYRNGVRVCHRRCL | - |
| 286 | Y5N+Y17H+N21M | GFCWNVCVYRNGVRVCHRRCM | - |
| 287 | Y5N+Y17H+N21P | GFCWNVCVYRNGVRVCHRRCP | - |
| 288 | Y5N+Y17H+N21Q | GFCWNVCVYRNGVRVCHRRCQ | - |
| 289 | Y5N+Y17H+N21R | GFCWNVCVYRNGVRVCHRRCR | 83 |
| 290 | Y5N+Y17H+N21S | GFCWNVCVYRNGVRVCHRRCS | - |
| 291 | Y5N+Y17H+N21W | GFCWNVCVYRNGVRVCHRRCW | 99 |
| 292 | Y5N+Y17H+N21Y | GFCWNVCVYRNGVRVCHRRCY | - |
| 293 | Y5N+Y17H+R19D | GFCWNVCVYRNGVRVCHRDCN | - |
| 294 | Y5N+Y17H+R19H | GFCWNVCVYRNGVRVCHRHCN | - |
| 295 | Y5N+Y17H+R19K | GFCWNVCVYRNGVRVCHRKCN | - |
| 296 | Y5N+Y17H+R19M | GFCWNVCVYRNGVRVCHRMCN | - |
| 297 | Y5N+Y17H+R19T | GFCWNVCVYRNGVRVCHRTCN | - |
| 298 | Y5N+Y17H+R19Y | GFCWNVCVYRNGVRVCHRYCN | - |
| 299 | Y5N+Y9A+Y17H | GFCWNVCVARNGVRVCHRRCN | 74 |
| 300 | Y5N+Y9D+Y17H | GFCWNVCVDRNGVRVCHRRCN | - |
| 301 | Y5N+Y9F+Y17H | GFCWNVCVFRNGVRVCHRRCN | - |
| 302 | Y5N+Y9G+Y17H | GFCWNVCVGRNGVRVCHRRCN | - |
| 303 | Y5N+Y9H+Y17H | GFCWNVCVHRNGVRVCHRRCN | 43 |
| 304 | Y5N+Y9I+Y17H | GFCWNVCVIRNGVRVCHRRCN | - |
| 305 | Y5N+Y9K+Y17H | GFCWNVCVKRNGVRVCHRRCN | 76 |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 306 | Y5N+Y9M+Y17H | GFCWNVCVMRNGVRVCHRRCN | - |
| 307 | Y5N+Y9Q+Y17H | GFCWNVCVQRNGVRVCHRRCN | - |
| 308 | Y5N+Y9R+Y17H | GFCWNVCVRRNGVRVCHRRCN | 94 |
| 309 | Y5N+Y9S+Y17H | GFCWNVCVSRNGVRVCHRRCN | - |
| 310 | Y5N+Y9T+Y17H | GFCWNVCVTRNGVRVCHRRCN | - |
| 311 | Y5N+Y9V+Y17H | GFCWNVCWRNGVRVCHRRCN | - |
| 312 | Y5N+Y9W+Y17H | GFCWNVCVWRNGVRVCHRRCN | - |
| 313 | Y5R+V13A+V15K | GFCWRVCVYRNGARKCYRRCN | 98 |
| 314 | Y5R+V13A+Y17S | GFCWRVCVYRNGARVCSRRCN | - |
| 315 | Y5R+V15K+Y17H | GFCWRVCVYRNGVRKCHRRCN | 93 |
| 316 | Y5R+V15S+Y17H | GFCWRVCVYRNGVRSCHRRCN | 90 |
| 317 | Y5R+V15S+Y17S | GFCWRVCVYRNGVRSCSRRCN | - |
| 318 | Y5R+V6A+G12S | GFCWRACVYRNSVRVCYRRCN | - |
| 319 | Y5R+V6A+V15A | GFCWRACVYRNGVRACYRRCN | 40 |
| 320 | Y5R+V6A+V15S | GFCWRACVYRNGVRSCYRRCN | 88 |
| 321 | Y5R+V6A+Y17H | GFCWRACVYRNGVRVCHRRCN | - |
| 322 | Y5R+V6A+Y9K | GFCWRACVKRNGVRVCYRRCN | - |
| 323 | Y5R+V6C+V15S | GFCWRCCVYRNGVRSCYRRCN | - |
| 324 | Y5R+V6S+Y17H | GFCWRSCVYRNGVRVCHRRCN | - |
| 325 | Y5R+V8A+V15S | GFCWRVCAYRNGVRSCYRRCN | - |
| 326 | Y5R+V8G+Y17H | GFCWRVCGYRNGVRVCHRRCN | - |
| 327 | Y5R+V8H+G12S | GFCWRVCHYRNSVRVCYRRCN | 98 |
| 328 | Y5R+V8H+V13K | GFCWRVCHYRNGKRVCYRRCN | - |
| 329 | Y5R+V8S+V13A | GFCWRVCSYRNGARVCYRRCN | - |
| 330 | Y5R+V8S+V13S | GFCWRVCSYRNGSRVCYRRCN | - |
| 331 | Y5R+V8S+V15K | GFCWRVCSYRNGVRKCYRRCN | 95 |
| 332 | Y5R+V8S+Y9R | GFCWRVCSRRNGVRVCYRRCN | - |
| 333 | Y5R+V8S+Y9S | GFCWRVCSSRNGVRVCYRRCN | - |
| 334 | Y5R+Y9R+V13A | GFCWRVCVRRNGARVCYRRCN | - |
| 335 | Y5R+Y9R+Y17H | GFCWRVCVRRNGVRVCHRRCN | 95 |
| 336 | Y5R+Y9S+Y17H | GFCWRVCVSRNGVRVCHRRCN | - |
| 337 | Y5R+Y9S+Y17S | GFCWRVCVSRNGVRVCSRRCN | - |
| 338 | V6A+G12S+V13K | GFCWYACVYRNSKRVCYRRCN | - |
| 339 | V6A+V13A+V15S | GFCWYACVYRNGARSCYRRCN | - |
| 340 | V6A+V13K+V15A | GFCWYACVYRNGKRACYRRCN | 98 |
| 341 | V6A+V13K+Y17H | GFCWYACVYRNGKRVCHRRCN | - |
| 342 | V6A+V15K+Y17H | GFCWYACVYRNGVRKCHRRCN | - |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 343 | V6A+V8A+V15A | GFCWYACAYRNGVRACYRRCN | 74 |
| 344 | V6R+V8H+R10S | GFCWYRCHYSNGVRVCYRRCN | - |
| 345 | V6S+Y9R+V15S | GFCWYSCVRRNGVRSCYRRCN | - |
| 346 | V6T+Y9K+V13L | GFCWYTCVKRNGLRVCYRRCN | 86 |
| 347 | V8A+R10K+Y17H | GFCWYVCAYKNGVRVCHRRCN | - |
| 348 | V8A+V15A+Y17H | GFCWYVCAYRNGVRACHRRCN | - |
| 349 | V8A+V15S+Y17H | GFCWYVCAYRNGVRSCHRRCN | - |
| 350 | V8A+Y9R+V13A | GFCWYVCARRNGARVCYRRCN | - |
| 351 | V8A+Y9R+V15S | GFCWYVCARRNGVRSCYRRCN | - |
| 352 | V8F+G12H+Y17H | GFCWYVCFYRNHVRVCHRRCN | - |
| 353 | Y9F+V15A+Y17H | GFCWYVCVFRNGVRACHRRCN | - |
| 354 | Y9K+V13A+Y17S | GFCWYVCVKRNGARVCSRRCN | - |
| 355 | Y9R+V15S+Y17S | GFCWYVCVRRNGVRSCSRRCN | - |
| 356 | R10K+V13K+V15S | GFCWYVCVYKNGKRSCYRRCN | - |
| 357 | V13K+V15A+Y17H | GFCWYVCVYRNGKRACHRRCN | - |
| 358 | G1R+Y5N+N11H+Y17H | RFCWNVCVYRHGVRVCHRRCN | - |
| 359 | G1R+Y5N+Y17H+R19H | RFCWNVCVYRNGVRVCHRHCN | 80 |
| 360 | W4A+V6A+Y9K+V13A | GFCAYACVKRNGARVCYRRCN | - |
| 361 | W4A+Y5H+V13A+V15K | GFCAHVCVYRNGARKCYRRCN | - |
| 362 | W4A+Y5H+Y9K+V13A | GFCAHVCVKRNGARVCYRRCN | 76 |
| 363 | W4A+Y5R+V8A+Y9K | GFCARVCAKRNGVRVCYRRCN | 80 |
| 364 | W4A+Y5R+Y9K+V15S | GFCARVCVKRNGVRSCYRRCN | - |
| 365 | W4A+Y5R+Y9R+V15K | GFCARVCVRRNGVRKCYRRCN | - |
| 366 | W4A+Y5R+Y9R+V15S | GFCARVCVRRNGVRSCYRRCN | - |
| 367 | W4F+V6A+Y9R+V15S | GFCFYACVRRNGVRSCYRRCN | - |
| 368 | W4F+V8A+Y9S+V15S | GFCFYVCASRNGVRSCYRRCN | - |
| 369 | W4F+Y5H+V8A+Y17H | GFCFHVCAYRNGVRVCHRRCN | - |
| 370 | W4F+Y5H+V8S+V15K | GFCFHVCSYRNGVRKCYRRCN | - |
| 371 | W4F+Y5N+V6A+V15S | GFCFNACVYRNGVRSCYRRCN | - |
| 372 | W4F+Y5N+V8A+Y9R | GFCFNVCARRNGVRVCYRRCN | - |
| 373 | W4F+Y5R+V15K+Y17H | GFCFRVCVYRNGVRKCHRRCN | - |
| 374 | W4F+Y5R+V15S+Y17S | GFCFRVCVYRNGVRSCSRRCN | - |
| 375 | W4F+Y5R+V6A+Y9K | GFCFRACVKRNGVRVCYRRCN | - |
| 376 | W4F+Y5R+V6S+V13A | GFCFRSCVYRNGARVCYRRCN | - |
| 377 | W4F+Y5R+V6S+Y9R | GFCFRSCVRRNGVRVCYRRCN | 65 |
| 378 | W4F+Y5R+V8A+V15K | GFCFRVCAYRNGVRKCYRRCN | - |
| 379 | W4F+Y5R+V8A+Y17H | GFCFRVCAYRNGVRVCHRRCN | - |
| 380 | W4F+Y5R+V8A+Y9S | GFCFRVCASRNGVRVCYRRCN | - |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 381 | W4F+Y5R+Y9K+V15K | GFCFRVCVKRNGVRKCYRRCN | 98 |
| 382 | W4F+Y9R+V15S+Y17H | GFCFYVCVRRNGVRSCHRRCN | - |
| 383 | W4G+Y5H+V15M+N21H | GFCGHVCVYRNGVRMCYRRCH | - |
| 384 | W4G+Y5K+Y9R+V13L | GFCGKVCVRRNGLRVCYRRCN | - |
| 385 | W4G+Y5R+V13K+V15A | GFCGRVCVYRNGKRACYRRCN | - |
| 386 | W4G+Y5R+V13K+V15A | GFCGRVCVYRNGKRACYRRCN | 81 |
| 387 | W4G+Y5R+V13K+V15S | GFCGRVCVYRNGKRSCYRRCN | - |
| 388 | W4G+Y5R+Y9R+V15K | GFCGRVCVRRNGVRKCYRRCN | - |
| 389 | W4T+Y5R+Y9R+V13L | GFCTRVCVRRNGLRVCYRRCN | - |
| 390 | Y5H+R10K+V13K+V15S | GFCWHVCVYKNGKRSCYRRCN | 87 |
| 391 | Y5H+V6A+Y9R+V15S | GFCWHACVRRNGVRSCYRRCN | - |
| 392 | Y5H+V8A+V13K+V15A | GFCWHVCAYRNGKRACYRRCN | - |
| 393 | Y5H+V8A+Y9K+V13L | GFCWHVCAKRNGLRVCYRRCN | - |
| 394 | Y5H+V8A+Y9R+V13A | GFCWHVCARRNGARVCYRRCN | 80 |
| 395 | Y5H+V8A+Y9R+Y17H | GFCWHVCARRNGVRVCHRRCN | - |
| 396 | Y5H+V8S+Y9K+V13L | GFCWHVCSKRNGLRVCYRRCN | 92 |
| 397 | Y5H+Y9R+V13A+V15K | GFCWHVCVRRNGARKCYRRCN | - |
| 398 | Y5H+Y9R+V13A+V15S | GFCWHVCVRRNGARSCYRRCN | - |
| 399 | Y5H+Y9R+V13A+Y17S | GFCWHVCVRRNGARVCSRRCN | - |
| 400 | Y5H+Y9S+V13L+V15K | GFCWHVCVSRNGLRKCYRRCN | - |
| 401 | Y5K+V6A+R10K+Y17H | GFCWKACVYKNGVRVCHRRCN | - |
| 402 | Y5K+V6A+V13A+V15S | GFCWKACVYRNGARSCYRRCN | - |
| 403 | Y5K+V6A+V8A+V13A | GFCWKACAYRNGARVCYRRCN | - |
| 404 | Y5K+Y9K+V13A+V15K | GFCWKVCVKRNGARKCYRRCN | - |
| 405 | Y5K+Y9R+V13A+Y17S | GFCWKVCVRRNGARVCSRRCN | - |
| 406 | Y5N+V6A+V8A+V13K | GFCWNACAYRNGKRVCYRRCN | - |
| 407 | Y5N+V6A+V8A+Y9R | GFCWNACARRNGVRVCYRRCN | 88 |
| 408 | Y5N+V6A+Y9R+V15S | GFCWNACVRRNGVRSCYRRCN | - |
| 409 | Y5N+V6F+N11Y+Y17H | GFCWNFCVYRYGVRVCHRRCN | - |
| 410 | Y5N+V8A+N11Q+Y17H | GFCWNVCAYRQGVRVCHRRCN | - |
| 411 | Y5N+V8A+V13K+V15A | GFCWNVCAYRNGKRACYRRCN | 86 |
| 412 | Y5N+Y9R+V13A+V15S | GFCWNVCVRRNGARSCYRRCN | - |
| 413 | Y5R+G12S+V13K+Y17H | GFCWRVCVYRNSKRVCHRRCN | - |
| 414 | Y5R+R10K+V13K+Y17H | GFCWRVCVYKNGKRVCHRRCN | - |
| 415 | Y5R+V6A+V13K+V15S | GFCWRACVYRNGKRSCYRRCN | - |
| 416 | Y5R+V6A+V15A+Y17H | GFCWRACVYRNGVRACHRRCN | - |
| 417 | Y5R+V6A+V8A+V13K | GFCWRACAYRNGKRVCYRRCN | 95 |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 418 | Y5R+V6A+V8A+V15A | GFCWRACAYRNGVRACYRRCN | 92 |
| 419 | Y5R+V6A+V8A+Y17H | GFCWRACAYRNGVRVCHRRCN | - |
| 420 | Y5R+V6A+V8A+Y9R | GFCWRACARRNGVRVCYRRCN | - |
| 421 | Y5R+V6A+V8H+V15S | GFCWRACHYRNGVRSCYRRCN | - |
| 422 | Y5R+V6A+Y9R+V15K | GFCWRACVRRNGVRKCYRRCN | - |
| 423 | Y5R+V6S+V13A+V15S | GFCWRSCVYRNGARSCYRRCN | - |
| 424 | Y5R+V8A+G12S+V15S | GFCWRVCAYRNSVRSCYRRCN | - |
| 425 | Y5R+V8A+R10S+V13K | GFCWRVCAYSNGKRVCYRRCN | 69 |
| 426 | Y5R+V8A+V13A+Y17H | GFCWRVCAYRNGARVCHRRCN | - |
| 427 | Y5R+V8A+V13K+V15A | GFCWRVCAYRNGKRACYRRCN | - |
| 428 | Y5R+V8A+V13K+Y17H | GFCWRVCAYRNGKRVCHRRCN | - |
| 429 | Y5R+V8A+V15A+Y17H | GFCWRVCAYRNGVRACHRRCN | - |
| 430 | Y5R+V8A+V15S+Y17H | GFCWRVCAYRNGVRSCHRRCN | - |
| 431 | Y5R+V8A+Y9K+V15K | GFCWRVCAKRNGVRKCYRRCN | - |
| 432 | Y5R+V8A+Y9K+V15S | GFCWRVCAKRNGVRSCYRRCN | - |
| 433 | Y5R+V8A+Y9K+Y17H | GFCWRVCAKRNGVRVCHRRCN | - |
| 434 | Y5R+V8A+Y9R+V15S | GFCWRVCARRNGVRSCYRRCN | - |
| 435 | Y5R+V8A+Y9S+V13L | GFCWRVCASRNGLRVCYRRCN | 85 |
| 436 | Y5R+V8G+G12S+V13K | GFCWRVCGYRNSKRVCYRRCN | - |
| 437 | Y5R+V8H+G12S+V13K | GFCWRVCHYRNSKRVCYRRCN | - |
| 438 | Y5R+V8H+R10K+V13K | GFCWRVCHYKNGKRVCYRRCN | - |
| 439 | Y5R+V8H+R10S+V13K | GFCWRVCHYSNGKRVCYRRCN | 92 |
| 440 | Y5R+V8S+Y9K+V15K | GFCWRVCSKRNGVRKCYRRCN | - |
| 441 | Y5R+Y9K+V13A+V15K | GFCWRVCVKRNGARKCYRRCN | - |
| 442 | Y5R+Y9K+V15S+Y17S | GFCWRVCVKRNGVRSCSRRCN | - |
| 443 | Y5R+Y9R+V13A+V15K | GFCWRVCVRRNGARKCYRRCN | - |
| 444 | Y5R+Y9R+V13A+V15S | GFCWRVCVRRNGARSCYRRCN | - |
| 445 | Y5R+Y9R+V13L+V15K | GFCWRVCVRRNGLRKCYRRCN | - |
| 446 | Y5R+Y9R+V13L+Y17H | GFCWRVCVRRNGLRVCHRRCN | - |
| 447 | Y5R+Y9R+V15S+Y17S | GFCWRVCVRRNGVRSCSRRCN | - |
| 448 | Y5R+Y9R+Y17S+R19H | GFCWRVCVRRNGVRVCSRHCN | - |
| 449 | Y5R+Y9S+V13A+Y17S | GFCWRVCVSRNGARVCSRRCN | - |
| 450 | V6A+V8A+Y9K+V13L | GFCWYACAKRNGLRVCYRRCN | 98 |
| 451 | V6A+Y9S+V13L+V15S | GFCWYACVSRNGLRSCYRRCN | - |
| 452 | V8A+R10S+V15S+Y17H | GFCWYVCAYSNGVRSCHRRCN | - |
| 453 | V8A+Y9R+V13L+V15S | GFCWYVCARRNGLRSCYRRCN | 92 |
| 454 | Y9K+V13A+V15K+Y17H | GFCWYVCVKRNGARKCHRRCN | 90 |
| 455 | W4A+Y5R+Y9K+V13A+V15K | GFCARVCVKRNGARKCYRRCN | - |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 456 | W4A+Y5R+Y9K+V13A+Y17H | GFCARVCVKRNGARVCHRRCN | - |
| 457 | W4A+Y5R+Y9S+V13L+V15K | GFCARVCVSRNGLRKCYRRCN | - |
| 458 | W4A+Y9S+V13A+V15S+Y17H | GFCAYVCVSRNGARSCHRRCN | - |
| 459 | W4F+Y5H+V8A+Y9R+V15K | GFCFHVCARRNGVRKCYRRCN | - |
| 460 | W4F+Y5H+V8A+Y9R+Y17H | GFCFHVCARRNGVRVCHRRCN | - |
| 461 | W4F+Y5H+Y9K+V15K+Y17S | GFCFHVCVKRNGVRKCSRRCN | - |
| 462 | W4F+Y5K+V8S+V13L+V15K | GFCFKVCSYRNGLRKCYRRCN | - |
| 463 | W4F+Y5K+V8S+Y9K+V15K | GFCFKVCSKRNGVRKCYRRCN | - |
| 464 | W4F+Y5N+V8A+Y9R+Y17S | GFCFNVCARRNGVRVCSRRCN | - |
| 465 | W4F+Y5R+V13A+V15K+Y17S | GFCFRVCVYRNGARKCSRRCN | - |
| 466 | W4F+Y5R+V6A+V8A+Y17H | GFCFRACAYRNGVRVCHRRCN | - |
| 467 | W4F+Y5R+V6A+V8T+Y9S | GFCFRACTSRNGVRVCYRRCN | - |
| 468 | W4F+Y5R+V6A+Y9K+V13A | GFCFRACVKRNGARVCYRRCN | - |
| 469 | W4F+Y5R+V6A+Y9R+Y17H | GFCFRACVRRNGVRVCHRRCN | - |
| 470 | W4F+Y5R+V6A+Y9S+V15S | GFCFRACVSRNGVRSCYRRCN | - |
| 471 | W4F+Y5R+V6S+V8A+Y9R | GFCFRSCARRNGVRVCYRRCN | - |
| 472 | W4F+Y5R+V6S+V8A+Y9S | GFCFRSCASRNGVRVCYRRCN | - |
| 473 | W4F+Y5R+V8A+V13A+V15S | GFCFRVCAYRNGARSCYRRCN | - |
| 474 | W4F+Y5R+V8A+V13A+Y17H | GFCFRVCAYRNGARVCHRRCN | - |
| 475 | W4F+Y5R+V8A+V13A+Y17S | GFCFRVCAYRNGARVCSRRCN | - |
| 476 | W4F+Y5R+V8A+V15K+Y17H | GFCFRVCAYRNGVRKCHRRCN | - |
| 477 | W4F+Y5R+V8A+Y9K+V13A | GFCFRVCAKRNGARVCYRRCN | - |
| 478 | W4F+Y5R+V8A+Y9K+V15K | GFCFRVCAKRNGVRKCYRRCN | - |
| 479 | W4F+Y5R+V8A+Y9K+Y17H | GFCFRVCAKRNGVRVCHRRCN | - |
| 480 | W4F+Y5R+V8A+Y9S+V15K | GFCFRVCASRNGVRKCYRRCN | - |
| 481 | W4F+Y5R+V8S+V13A+V15S | GFCFRVCSYRNGARSCYRRCN | - |
| 482 | W4F+Y5R+V8S+V13L+V15K | GFCFRVCSYRNGLRKCYRRCN | - |
| 483 | W4F+Y5R+V8S+Y9K+V13A | GFCFRVCSKRNGARVCYRRCN | - |
| 484 | W4F+Y5R+V8S+Y9K+Y17H | GFCFRVCSKRNGVRVCHRRCN | - |
| 485 | W4F+Y5R+V8S+Y9R+V13L | GFCFRVCSRRNGLRVCYRRCN | - |
| 486 | W4F+Y5R+V8S+Y9S+V13A | GFCFRVCSSRNGARVCYRRCN | - |
| 487 | W4F+Y5R+V8S+Y9S+V15K | GFCFRVCSSRNGVRKCYRRCN | - |
| 488 | W4F+Y5R+Y9K+V13A+V15S | GFCFRVCVKRNGARSCYRRCN | - |
| 489 | W4F+Y5R+Y9R+V15K+Y17S | GFCFRVCVRRNGVRKCSRRCN | - |
| 490 | W4F+Y9S+V13A+V15K+Y17H | GFCFYVCVSRNGARKCHRRCN | - |
| 491 | W4G+Y5K+Y9K+V13L+V15K | GFCGKVCVKRNGLRKCYRRCN | - |
| 492 | W4G+Y5R+G12S+V13K+V15S | GFCGRVCVYRNSKRSCYRRCN | - |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 493 | W4G+Y5R+R10K+V13K+V15A | GFCGRVCVYKNGKRACYRRCN | 77 |
| 494 | W4S+V6S+V8A+V13S+V15S | GFCSYSCAYRNGSRSCYRRCN | - |
| 495 | W4S+Y5N+V6S+Y9K+Y17S | GFCSNSCVKRNGVRVCSRRCN | - |
| 496 | W4T+Y5N+V8A+Y9K+V13A | GFCTNVCAKRNGARVCYRRCN | - |
| 497 | Y5H+V6A+Y9R+V13A+V15S | GFCWHACVRRNGARSCYRRCN | - |
| 498 | Y5H+V6A+Y9R+V13L+V15K | GFCWHACVRRNGLRKCYRRCN | - |
| 499 | Y5H+V6A+Y9R+V13L+Y17H | GFCWHACVRRNGLRVCHRRCN | - |
| 500 | Y5H+V8A+R10K+V15A+Y17H | GFCWHVCAYKNGVRACHRRCN | - |
| 501 | Y5H+V8A+Y9R+V13L+Y17S | GFCWHVCARRNGLRVCSRRCN | - |
| 502 | Y5K+V6R+V13L+V15K+Y17H | GFCWKRCVYRNGLRKCHRRCN | - |
| 503 | Y5K+V6S+Y9R+V13L+V15S | GFCWKSCVRRNGLRSCYRRCN | - |
| 504 | Y5K+V8A+Y9R+V13A+V15S | GFCWKVCARRNGARSCYRRCN | 95 |
| 505 | Y5K+V8S+Y9S+V13L+V15S | GFCWKVCSSRNGLRSCYRRCN | - |
| 506 | Y5K+Y9S+V13A+V15K+Y17S | GFCWKVCVSRNGARKCSRRCN | - |
| 507 | Y5N+V8A+Y9R+V13L+Y17H | GFCWNVCARRNGLRVCHRRCN | - |
| 508 | Y5N+Y9R+V13L+V15K+Y17H | GFCWNVCVRRNGLRKCHRRCN | - |
| 509 | Y5R+R10S+V13K+V15S+Y17H | GFCWRVCVYSNGKRSCHRRCN | 87 |
| 510 | Y5R+V6A+R10K+G12S+V13K | GFCWRACVYKNSKRVCYRRCN | -<br>- |
| 511 | Y5R+V6A+R10K+V15A+Y17H | GFCWRACVYKNGVRACHRRCN | - |
| 512 | Y5R+V6A+V8A+V13K+V15A | GFCWRACAYRNGKRACYRRCN | - |
| 513 | Y5R+V6A+V8A+V13K+V15S | GFCWRACAYRNGKRSCYRRCN | - |
| 514 | Y5R+V6A+V8A+Y9S+Y17H | GFCWRACASRNGVRVCHRRCN | - |
| 515 | Y5R+V6A+V8S+Y9R+V13L | GFCWRACSRRNGLRVCYRRCN | - |
| 516 | Y5R+V6A+Y9K+V13A+Y17S | GFCWRACVKRNGARVCSRRCN | - |
| 517 | Y5R+V6A+Y9K+V13L+V15S | GFCWRACVKRNGLRSCYRRCN | - |
| 518 | Y5R+V6A+Y9R+V13A+V15S | GFCWRACVRRNGARSCYRRCN | - |
| 519 | Y5R+V6A+Y9R+V13L+V15S | GFCWRACVRRNGLRSCYRRCN | - |
| 520 | Y5R+V6A+Y9S+V13A+V15S | GFCWRACVSRNGARSCYRRCN | - |
| 521 | Y5R+V6A+Y9S+V13L+Y17S | GFCWRACVSRNGLRVCSRRCN | - |
| 522 | Y5R+V6R+Y9R+V13A+V15S | GFCWRRCVRRNGARSCYRRCN | - |
| 523 | Y5R+V8A+R10K+V13K+V15S | GFCWRVCAYKNGKRSCYRRCN | 90 |
| 524 | Y5R+V8A+Y9R+V13L+Y17H | GFCWRVCARRNGLRVCHRRCN | - |
| 525 | Y5R+V8A+Y9S+V13A+Y17S | GFCWRVCASRNGARVCSRRCN | - |
| 526 | Y5R+V8G+R10K+V15A+Y17H | GFCWRVCGYKNGVRACHRRCN | - |
| 527 | Y5R+V8G+V13K+V15A+Y17H | GFCWRVCGYRNGKRACHRRCN | - |
| 528 | Y5R+V8S+R10S+G12S+V13K | GFCWRVCSYSNSKRVCYRRCN | - |
| 529 | Y5R+V8S+Y9R+V13L+V15S | GFCWRVCSRRNGLRSCYRRCN | - |

| SEQ ID NO: | Substitution | Amino acid sequence | Protein binding (%) |
|---|---|---|---|
| 530 | Y5R+Y9R+V13L+V15S+Y17S | GFCWRVCVRRNGLRSCSRRCN | - |
| 531 | Y5R+Y9S+V13A+V15K+Y17S | GFCWRVCVSRNGARKCSRRCN | - |
| 532 | Y5R+Y9S+V13L+V15S+Y17S | GFCWRVCVSRNGLRSCSRRCN | - |
| 533 | F2L+Y5R+V8A+R10S+V13K+V15A | GLCWRVCAYSNGKRACYRRCN | - |
| 534 | W4F+Y5N+Y9S+V13A+V15K+Y17H | GFCFNVCVSRNGARKCHRRCN | - |
| 535 | W4F+Y5R+V6A+V8A+Y9R+V15S | GFCFRACARRNGVRSCYRRCN | - |
| 536 | W4F+Y5R+V6A+V8S+Y9K+V13L | GFCFRACSKRNGLRVCYRRCN | - |
| 537 | W4F+Y5R+V6A+Y9K+V13L+V15K | GFCFRACVKRNGLRKCYRRCN | - |
| 538 | W4F+Y5R+V6A+Y9K+V13L+Y17H | GFCFRACVKRNGLRVCHRRCN | - |
| 539 | W4F+Y5R+V8A+Y9K+V13A+V15S | GFCFRVCAKRNGARSCYRRCN | - |
| 540 | W4F+Y5R+V8A+Y9S+V15K+Y17H | GFCFRVCASRNGVRKCHRRCN | - |
| 541 | W4F+Y5R+V8S+Y9K+V13A+V15K | GFCFRVCSKRNGARKCYRRCN | - |
| 542 | W4G+Y5H+V6R+V8S+Y9R+V15K | GFCGHRCSRRNGVRKCYRRCN | - |
| 543 | W4S+Y5H+V6R+V8S+G12S+V15A | GFCSHRCSYRNSVRACYRRCN | - |
| 544 | W4S+Y5R+V8S+V13S+V15A+Y17H | GFCSRVCSYRNGSRACHRRCN | - |
| 545 | Y5R+V6A+V8A+Y9S+V13L+Y17S | GFCWRACASRNGLRVCSRRCN | - |
| 546 | W4S+Y5N+V6R+V8H+R10S+V13S+V15A +Y17H | GFCSNRCHYSNGSRACHRRCN | - |
| 547 | Y5G+V6A+C7V+V8N+R10T+N11S+G12N +V13C+V15A+Y17K | GFCWGAVNYTSNCRACKRRCN | - |
| 548 | F2S+Y5G+V6A+C7V+V8N+R10T+N11S+ G12N+V13C+V15A+Y17K | GSCWGAVNYTSNCRACKRRCN | - |

**EXAMPLE 2**

**Efficacy of NZ17074 against *Escherichia coli* AID#172 in the neutropenic murine peritonitis/sepsis model and estimation of ED50**

**Introduction**

**[0135]** The purpose of this study was to investigate the dose-response relationship following intravenous (i.v.) administration of a single dose of NZ17074 ranging from 0.16 - 12 mg/kg. The effect was tested against *E. coli* AID#172 in the neutropenic peritonitis model. Treatment with 40 mg/kg meropenem was included as a positive control group. The colony counts in blood and peritoneal fluid were determined at 5 hrs after treatment.

**[0136]** The murine peritonitis/sepsis model is a well-recognized model for studies of antimicrobial activity

as described by N. Frimodt-Møller and J.D. Knudsen in Handbook of Animal Models of Infection (1999), ed. by O. Zak & M. A. Sande, Academic Press, San Diego, US.

**Materials and Methods**

**[0137]**

• 30 outbred, NMRI female mice, 25-30 gram (Harlan Scandinavia)

• *Escherichia. coli* AID#172 from Statens Serum Instute, Copenhagen, Denmark. Clinical isolate from a human wound from 2003. Multiresistant (Ampicillin, Ceftazidime, Aztreonam, Gentamicin, Ciprofloxacin)

• NZ17074 in Ringer Acetate, pH 6: 1.2 mg/ml, 6.0 ml. The solution was stored at 4°C until use. Analyses of the dose formulations used were performed after completion of the in-life phase of the study and gave the following results:

| Intended concentration | Measured concentration |
|---|---|
| 1.2 mg/ml | 1.11 mg/ml |
| 0.6 mg/ml | 0.51 mg/ml |
| 0.3 mg/ml | 0.24 mg/ml |
| 0.15 mg/ml | 0.14 mg/ml |
| 0.075 mg/ml | 0.043 mg/ml |
| 0.03 mg/ml | 0.010 mg/ml |
| 0.016 mg/ml | 0.002 mg/ml |

• Vehicle (Ringer Acetate pH 6). The solution was stored at 4°C until use

• Meronem® (AstraZeneca, 500 mg infusion substance, meropenem). Lot no. 09466C Date of expire: 08-2013

• Water, sterile

• 0.9% saline, sterile

• Cyclophosphamide, Apoda$^{n}$® (A-Pharma, 1 g) Batch nr. 928491 Date of expire: 05-2012

• 5% Horse Blood Agar plates

• Lactose bromthymol blue agar plates

**Laboratory animal facilities and housing of mice**

**[0138]** The temperature and humidity were registered daily in the animal facilities. The temperature was 21°C +/- 2°C and can be regulated by heating and cooling. The humidity was 55 +/- 10%. The air changes per hour were approximately 10-20 times, and light/dark period was in 12-hours interval of 6 a.m.- 6 p.m./6 p.m - 6 a.m.

**[0139]** The mice had free access to domestic quality drinking water and food (2016, Harlan). The mice were housed in Type 3 macrolone cages with 3 mice/cage. The bedding was Aspen Wood from Tapvei. Further the animals were offered paper strands from Sizzle-nest as nesting material. Mice were marked on the tail for individual identification within the cage. Mice were weighed the day before dosing

**Preparation of NZ17074 solutions**

**[0140]** The solution of 1.2 mg/ml was further diluted in PBS vehicle as follows:

| | |
|---|---|
| 0.6 mg/ml ~ 7.5 mg/kg: | 1.5 ml of 1.2 mg/ml NZ17074 + 1.5 ml vehicle |
| 0.3 mg/ml ~ 5.0 mg/kg: | 1.5 ml of 0.6 mg/ml NZ17074 + 1.5 ml vehicle |
| 0.15 mg/ml ~ 2.5 mg/kg: | 1.5 ml of 0.3 mg/ml NZ17074 + 1.5 ml vehicle |
| 0.075 mg/ml ~ 1.25 mg/kg: | 1.5 ml of 0.15 mg/ml NZ17074 +1.5 ml vehicle |
| 0.03 mg/ml ~ 0.63 mg/kg: | 1.5 ml of 0.075 mg/ml NZ17074 +2.25 ml vehicle |
| 0.016 mg/ml ~ 0.16 mg/kg: | 1.5 ml of 0.03 mg/ml NZ17074 +1.5 ml vehicle |

**Preparation meropenem solution**

**[0141]** Treatment with meropenem 40 mg/kg was included as a positive control group. A total of 500 mg meropenem (one ampoule) was dissolved in 10 ml water ~ 50 mg/ml This stock solution was further diluted to 4 mg/ml (0.4 ml 50 mg/ml + 4.6 ml saline).

**Preparation of cyclophosphamide**

**[0142]** A total of 1 g cyclophosphamide (one ampoule Apodan 1 g) was dissolved in 50 ml water ~ 20 mg/ml on each day of use. This stock solution was further diluted to 11 mg/ml (16.5 ml 20 mg/ml + 13.5 ml saline) for use on day -4 or to 5 mg/kg (8.25 ml 20 mg/ml + 21.75 ml saline)) for use on day -1.

**Treatment of mice with cyclophosphamide**

**[0143]** The mice were rendered neutropenic by injecting 0.5 ml cyclophosphamide solution intraperitoneally 4 days (200 mg/kg) and 1 day (100 mg/kg) prior to inoculation.

**Inoculation of mice**

**[0144]** Fresh overnight *E. coli* AID#172 colonies from a 5% Horse Blood Agar plate were suspended and diluted in sterile saline to approximately 2 x$10^6$ CFU/ml. One hour before start of treatment (time -1 hr) mice were inoculated intraperitoneally with 0.5 ml of the *E. coli* suspension in the lateral lower quadrant of the abdomen. Approximately ½-1 hrs after treatment, mice were treated orally with 45 I neurophen (20 mg ibuprofen/ml corresponding to 30 mg/kg) as a pain relief.

**Treatment of mice**

**[0145]** The mice were treated i.v. in the lateral tail vein over approximately 30 seconds with 10 ml/kg with a single dose of NZ17074, meropenem or vehicle at time 0 hr (see Table 1). The dosing was based on a mean weight of 30 g. Mice that weighed 28-32 g received 0.30 ml solution. Mice that weighed 27-28 g received 0.25 ml solution and mice that weighed 32.1-36 g received 0.35 ml solution.

**Table 1. Treatment and sampling schedule in the murine peritonitis model.**

| Inoculation i.p. at - 1 hr | Intravenous treatment at 0 hr | Sampling and mouse no. | |
|---|---|---|---|
| | | 0 hr | 5 hrs |
| 0.5 ml of *E. coli* AID# 172 1x$10^6$ CFU/ml | Vehicle, Ringer acetate | | 1-2-3 |
| | NZ17074 0.16 mg/kg | | **4-5-6** |
| | NZ17074 0.30 mg/kg | | **7-8-9** |
| | NZ17074 0.75 mg/kg | | **10-11-12** |
| | NZ17074 1.5 mg/kg | | **13-14-15** |
| | NZ17074 3.0 mg/kg | | **16-17-18** |
| | NZ 17074 6.0 mg/kg | | **19-20-21** |
| | NZ17074 12 mg/kg | | **22-23-24** |
| | meropenem 40 mg/kg | | **25-26-27** |
| | No treatment | **28-29-30** | |
| T indicates the time in relation to treatment. Numbers in the sampling columns are mouse identification numbers. | | | |

**Clinical Scoring of mice**

**[0146]** The mice were observed during the study and scored 0-5 based on their behaviour and clinical signs.

| | |
|---|---|
| Score 0: | Healthy. |
| Score 1: | Minor clinical signs of infection and inflammation e.g. observations of minor signs of distress or changed activity. |
| Score 2: | Clear signs of infection like, social withdrawal, lack of curiosity, changed body position, piloerection, or changes in pattern of movement. |
| Score 3: | Severe signs of infection like stiff movements, lack of curiosity, changed body position, piloerection, pain, or changes in pattern of movement. |
| Score 4: | Severe pain and the mouse was sacrificed immediately to minimize the suffering of the animal. |
| Score 5: | The mouse was dead. |

**Sampling**

**[0147]** Colony counts were determined from blood and peritoneal fluid at 0 and 5 hrs. The mice were anaesthetized with $CO_2$ + $O_2$ and blood was collected from axillary cutdown in 1.5 ml EDTA coated eppendorf tubes. The mice were sacrificed immediately after blood sampling and a total of 2 ml sterile saline was injected i.p. and the abdomen gently massaged before it was opened and fluid sampled with a pipette. Each sample was then 10 fold diluted in saline and 20-µl spots were applied on blue agar plates. All agar plates were incubated 18-22 hrs at 35°C in ambient air.

**Results**

**[0148]** The colony counts were performed at the start of treatment and 5 hrs after treatment. The CFU counts and the clinical score of the mice are shown in Table 3. The CFU numbers are $\log_{10}$ transformed before performing calculations.

**[0149]** The CFU/ml in the inoculum was determined to 6.29 $\log_{10}$. At start of treatment the mean $\log_{10}$ CFU/ml in peritoneal fluid was 5.76 and in blood 5.13 and the CFU levels remained at a similar level in the vehicle group (5.72 and 4.65 $\log_{10}$ CFU/ml in the peritoneum and blood respectively) at 5 hrs after treatment. Slightly lower CFU levels were observed in blood and peritoneal fluid after treatment with NZ17074 0.16-3.0 mg/kg. Treatment with 6 and 12 mg/kg NZ17074 resulted in CFU levels significantly lower ($p<0.001$) than after vehicle treatment both in peritoneal fluid and in blood (Table 3). Also the meropenem treatment, 40 mg/kg, resulted in significant reduction compared to the vehicle treated mice both in blood ($p<0.05$) and peritoneal fluid ($p<0.01$).

**[0150]** The dose-response curves (data not shown) were calculated in GraphPad Prism using Sigmoidal dose-response (variable slope). From these ED50 values were determined to 3.09±2.07 mg/kg in peritoneal fluid and 3.17±0.53 mg/kg in blood.

**[0151]** The maximum effect of NZ17074, $E_{max}$, was defined as the log CFU difference between no response and maximum response. No response was characterised as colony counts at the same level as determined for vehicle treated mice. The $E_{max}$ was calculated as the difference between the "Top plateau" and "Bottom plateau" in GraphPad Prism using Sigmoidal dose-response to be 4.72 $\log_{10}$ CFU for the peritoneal fluid and 3.15 $\log_{10}$ CFU for the blood.

**[0152]** In addition the 1, 2 and 3 log killing, defined as the dose required to obtain 1, 2 or 3 log reduction in bacterial loads compared to start of treatment, were estimated using GraphPad Prism. The 1, 2 and 3 log killing of NZ17074 was 1.11 mg/kg, 2.95mg/kg and 4.73 mg/kg respectively in peritoneal fluid and 0.25 mg/kg, 2.75 mg/kg and 3.78 mg/kg respectively in blood.

**[0153]** No or only mild clinical score was observed in all of the treatment groups (Table 3).

**Discussion and conclusion**

**[0154]** The purpose of this study was to investigate the dose-response relationship following intravenous (i.v.) administration of a single dose of NZ17074 ranging from 0.16 - 12 mg/kg. The effect was tested against *E. coli* AID#172 in the neutropenic peritonitis/sepsis model.

**[0155]** The ED50 values for NZ17074 were determined to 3.09±2.07 mg/kg in the peritoneal fluid and 3.17±0.53 mg/kg in the blood. The 1 log killing was estimated to be 1.11 mg/kg in the peritoneal fluid and 0.25 mg/kg in the blood. The 2 log killing was estimated to be 2.95 mg/kg in the peritoneal fluid and 2.76 mg/kg in the blood. The 3 log killing was estimated to be 4.73 mg/kg in the peritoneal fluid and 3.78 mg/kg in the blood.

**Table 2.** Efficacy values for NZ17074 against *E. coli* AID#172 calculated in Graph Pad Prism.

| NZ17074 | Peritoneal fluid | Blood |
|---|---|---|
| TOP | 0.325 CFU/ml | -0.985 CFU/ml |

| NZ17074 | Peritoneal fluid | Blood |
|---|---|---|
| BOTTOM | -4.486CFU/ml | -4.138 CFU/ml |
| Emax | 4.811 CFU/ml | 3.153 CFU/ml |
| ED50 | 3.086 mg/kg | 3.168 mg/kg |
| $R^2$ | 0.7524 | 0.6889 |
| 1 log killing | 1.11 mg/kg | 0.25 mg/kg |
| 2 log killing | 2.95 mg/kg | 2.76 mg/kg |
| 3 log killing | 4.73 mg/kg | 3.78 mg/kg |

**Table 3.** Colony counts of *E. coli* AID#172 in blood and peritoneal fluid from neutropenic mice treated with a single dose of NZ17074, meropenem or vehicle.

| Treatment T = 0 hr | Mouse no. | Time | Clinical score | | $log_{10}$ CFU | | | |
|---|---|---|---|---|---|---|---|---|
| | | | T=0hr | T=5hrs | PF | mean PF | Blood | mean Blood |
| Vehicle | 1 | T = 5 | 1 | 1 | 5.74 | 5.72 | 5.05 | 4.65 |
| | 2 | T = 5 | 1 | 0 | 5.54 | | 4.78 | |
| | 3 | T = 5 | 1 | 1 | 5.88 | | 4.11 | |
| NZ17074 0.16 mg/kg | 4 | T = 5 | 1 | 1 | 5.16 | 5.31 | 4.27 | 4.54 |
| | 5 | T = 5 | 1 | 1 | 4.78 | | 4.19 | |
| | 6 | T = 5 | 1 | 0 | 5.98 | | 5.16 | |
| NZ17074 0.30 mg/kg | 7 | T = 5 | 1 | 0 | 2.76 | 4.26 | 1.40 | 2.88 |
| | 8 | T = 5 | 1 | 1 | 5.74 | | 4.63 | |
| | 9 | T = 5 | 1 | 0 | 4.27 | | 2.60 | |
| NZ17074 0.75 mg/kg | 10 | T = 5 | 1 | 0 | 5.74 | 5.16 | 5.07 | 4.46 |
| | 11 | T = 5 | 1 | 1 | 4.95 | | 4.30 | |
| | 12 | T = 5 | 1 | 1 | 4.78 | | 4.00 | |
| NZ17074 1.5 mg/kg | 13 | T = 5 | 1 | 0 | 3.33 | 4.41 | 3.51 | 3.99 |
| | 14 | T = 5 | 1 | 1 | 4.72 | | 3.92 | |
| | 15 | T = 5 | 1 | 0 | 5.18 | | 4.54 | |
| NZ17074 3.0 mg/kg | 16 | T = 5 | 1 | 1 | 4.74 | 3.91 | 3.86 | 2.81 |
| | 17 | T = 5 | 1 | 1 | 4.74 | | 3.57 | |
| | 18 | T = 5 | 1 | 0 | 2.24 | | 1.00 | |
| NZ17074 6.0 mg/kg | 19 | T = 5 | 1 | 1 | 2.18 | 2.12 *** | 1.00 | 1.00 *** |
| | 20 | T = 5 | 1 | 1 | 2.18 | | 1.00 | |
| | 21 | T = 5 | 1 | 1 | 2.00 | | 1.00 | |
| NZ17074 12 mg/kg | 22 | T = 5 | 1 | 1 | 1.00 | 1.36 *** | 1.00 | 1.00 *** |
| | 23 | T = 5 | 1 | 0 | 1.69 | | 1.00 | |
| | 24 | T = 5 | 1 | 0 | 1.40 | | 1.00 | |
| Meropenem 40 mg/kg | 25 | T = 5 | 1 | 1 | 3.92 | 2.64 ** | 2.48 | 2.38 * |
| | 26 | T = 5 | 1 | 1 | 1.70 | | 1.70 | |
| | 27 | T = 5 | 1 | 0 | 2.30 | | 2.95 | |

| Treatment T = 0 hr | Mouse no. | Time | Clinical score | | $log_{10}$ CFU | | | |
|---|---|---|---|---|---|---|---|---|
| | | | T=0hr | T=5hrs | PF | mean PF | Blood | mean Blood |
| None | 28 | T = 0 | 1 | | 5.84 | 5.76 | 5.08 | 5.13 |
| | 29 | T = 0 | 1 | | 5.78 | | 4.98 | |
| | 30 | T = 0 | 1 | | 5.65 | | 5.34 | |
| Stars indicates significantly different from vehicle group (Anova; multiple comparison). * corresponds to $p<0.05$; ** corresponds to $p<0.01$ *** corresponds to $p<0.001$. Detection limit 1.4 $log_{10}$ CFU/ml. Samples with no detectable bacteria is presented as 1.0 $log_{10}$ CFU/ml. | | | | | | | | |

**EXAMPLE 3**

**Peritonitis/sepsis model: Effect over time of 7.5 mg/kg NZ17074 against *Escherichia coli* AID#172 in neutropenic NMRI mice**

**Introduction**

**[0156]** The purpose of this study was to investigate the *in vivo* efficacy of NZ17074 following intravenous (i.v.) administration of a single dose of 7.5 mg/kg. The effect was tested against *Escherichia coli* AID#172 in the peritonitis model in neutropenic NMRI mice to avoid the use of mucin as normally applied in the murine peritonitis model. The mice were rendered neutropenic by cyclophosphamide injections. Treatment with 40 mg/kg meropenem was included as a positive control group and treatment with vehicle was included as a negative control group. The colony counts in peritoneal fluid and blood were determined at 2 and 5 hrs after treatment.

**Materials and Methods**

**[0157]**

- 30 outbred, NMRI female mice, 28-32 gram (Harlan Scandinavia)
- *Escherichia coli* AID#172 from Statens Serum Instute, Copenhagen, Denmark. Clinical isolate from a human wound from 2003. Multiresistant (Ampicillin, Ceftazidime, Aztreonam, Gentamicin, Ciprofloxacin)
- NZ17074 in Ringer Acetate pH 6, 1.2 ml 0.75 mg/ml. Analyses of the dose formulation performed after the study showed a concentration of approx. 0.78 mg/ml.
- Vehicle (Ringer Acetate pH 6) 3 ml.
- Meronem®(AstraZeneca, 500 mg meropenem infusionsubstance). Lot no. 09466C Date of expire: 08-2013
- Apodan®(A-Pharma, 1 g cyclophosphamide) Batch nr. 928491 Date of expire: 05-2012
- Water, sterile
- 0.9 % saline, sterile
- 5 % Horse Blood Agar plates

- Lactose bromthymol blue agar plates

**Laboratory animal facilities and housing of mice**

**[0158]** The temperature and humidity were registered daily in the animal facilities. The temperature was 21 °C +/- 2°C and can be regulated by heating and cooling. The humidity was 55 +/- 10%. The air changes per hour were approximately 10-20 times, and light/dark period was in 12-hours interval of 6 a.m. - 6 p.m./6 p.m. - 6 a.m. The mice had free access to domestic quality drinking water and food (2016, Harlan). The mice were housed in Type 3 macrolone cages with 3 mice/cage. The bedding was Aspen Wood from Tapvei. Further the animals were offered paper strands from Sizzle-nest as nesting material. Mice were marked on the tail for individual identification within the cage.

**NZ17074 solution**

**[0159]** A solution of 0.75 mg/ml of each test compound was stored at +4°C until one hour before injection, thereafter at room temperature.

**Preparation of meropenem solution**

**[0160]** A total of 500 mg meropenem (one ampoule) was dissolved in 10 ml water ~ 50 mg/ml the day of use. This stock solution was further diluted to 4 mg/ml (0.4 ml 50 mg/ml + 4.6 ml saline).

**Preparation of cyclophosphamide**

**[0161]** A total of 1 g cyclophosphamide (one ampoule Apodan) was dissolved in 50 ml water ~ 20 mg/ml on each day of use. This stock solution was further diluted to 11 mg/ml (16.5 ml of 20 mg/ml + 13.5 ml saline) for use on day -4 or to 5.5 mg/ml (8.25 ml of 20 mg/ml + 21.75 ml saline) for use on day -1.

**Treatment of mice with cyclophosphamide**

**[0162]** The mice were rendered neutropenic by injecting 0.5 ml cyclophosphamide solution intraperitoneally 4 days (200 mg/kg) and 1 day (100 mg/kg) prior to inoculation.

**Inoculation of mice**

**[0163]** Fresh overnight *E. coli* AID#172 colonies from a 5% Horse Blood Agar plate were suspended and diluted in sterile saline to approximately 2 $x10^6$ CFU/ml.

**[0164]** One hour before start of treatment (time -1 hr) mice were inoculated intraperitoneally with 0.5 ml of the *E. coli* suspension in the lateral lower quadrant of the abdomen.

**[0165]** 2.5 hrs after treatment, when clinical signs of infection were significant, mice were treated orally with 45 l neurophen (20 mg ibuprofen/ml, corresponding to 30 mg/kg) as a pain relief.

**Scoring of mice**

**[0166]** The mice were clinically scored for signs of infection at the time of each sampling.

| | |
|---|---|
| Score 0: | Healthy. |
| Score 1: | Minor clinical signs of infection and inflammation e.g. observations of minor signs of distress or changed activity. |
| Score 2: | Clear signs of infection like, social withdrawal, lack of curiosity, changed bod; position, piloerection, or changes in pattern of movement. |
| Score 3: | Severe signs of infection like stiff movements, lack of curiosity, forced ventilation, changed body position, piloerection, pain, or changes in pattern o movement. |
| Score 4: | Severe pain and the mouse was sacrificed immediately to minimize the suffering of the animal. |
| Score 5: | The mouse was dead. |

**Treatment of mice**

**[0167]** The mice were treated i.v. in the lateral tail vein over approximately 30 seconds with a single dose of NZ17074, meropenem or vehicle at time 0 hr (see Table 1). The dosing was based on a mean weight of 30 g. Mice that weighed 28-32 g received 0.30 ml solution. Mice that weighed 27-28 g received 0.25 ml solution and mice that weighed 32,1-36 g received 0.35 ml solution. Mouse 17 accidently received 0.35 ml although it weighed 29.5 g. This does not seem to have influenced the results as the CFU levels in this mouse was very similar to the other two mice in the group.

**Table 4.** Treatment and sampling schedule in the murine peritonitis model.

| **Inoculation T = -1 hr** | **Treatment T = 0 hr** | **Sampling T = 0 hr** | **Sampling T = 2 hrs** | **Sampling T = 5 hrs** |
|---|---|---|---|---|
| 0.5 ml of *E. coli* AID# 172 $10^6$ CFU/ml | NZ17074 | | | 4,5,6 |
| | Meropenem | | | 7,8,9 |
| | Vehicle (Ringer Acetate) | | | 10,11,12 |
| | NZ17074 | | 16,17,18 | |
| | Meropenem | | 19,20,21 | |
| | Vehicle (Ringer Acetate) | | 22,23,24 | |
| | None | | 25,26,27 | |
| | None | 28,29,30 | | |

T indicates the time in relation to treatment. Numbers in the sampling columns are mouse identification numbers.

**Sampling**

**[0168]** Colony counts were determined from blood and peritoneal fluid at 0, 2 and 5 hrs after treatment according to Table 1.

**[0169]** The mice were anesthetized with $O_2$ + $CO_2$ and blood was collected by axilliary cut down. The mice were sacrificed by cervical dislocation and a total of 2 ml sterile saline was injected i.p. and the abdomen gently massaged before it was opened and fluid sampled with a pipette. Each sample was 10 fold diluted in saline and 20-µl spots were applied on blood agar plates. All agar plates were incubated 18-22 hrs at 35°C in ambient air.

**Results**

**[0170]** The colony counts and the clinical scores of the mice are shown in Table 2. The CFU numbers are $\log_{10}$ transformed before performing calculations to obtain a normal distribution.

**[0171]** The CFU/ml in the inoculum was determined to 6.30 $\log_{10}$. At start of treatment the mean $\log_{10}$ CFU/ml in the peritoneal fluid was 3.57 and in the blood 3.54 and the CFU level increased to 5.43 and 4.58 in the peritoneal fluid and the blood respectively after 2 hrs in vehicle treated animals and to 5.72 and 4.74 in the peritoneal fluid and the blood respectively after 5 hrs in vehicle treated mice, which was as expected.

**[0172]** At 2 hrs after treatment with NZ17074 significantly lower CFU levels were observed both in the blood and the peritoneal fluid compared to the vehicle treatment ($p< 0.001$).

**[0173]** A further reduction of the CFU levels was observed at 5 hrs after treatment with NZ17074 both in the blood and in the peritoneal fluid ($p< 0.001$ compared to vehicle control). The CFU levels were more the 3 $\log_{10}$ CFU/ml lower than after vehicle treatment.

**[0174]** Also meropenem treatment resulted in significantly ($p< 0.01$) reduced CFU levels compared to vehicle treatment in the peritoneal fluid at both 2 and 5 hrs after treatment but in the blood only at 5 hrs after treatment. The lack of significance in the blood at 2 hrs after treatment may reflect the large variability in the vehicle group rather than poor effect of meropenem.

**[0175]** The difference in CFU levels after NZ17074 or meropenem treatment compared to vehicle treatment was:

| | | | |
|---|---|---|---|
| NZ17074, 7.5 mg/kg | 2 hrs: | peritoneum -1.63 log cfu/ml | blood -2.50 log cfu/ml |
| | 5 hrs: | peritoneum -3.76 log cfu/ml | blood -3.74 log cfu/ml |
| Meropenem 40 mg/kg | 2 hrs: | peritoneum -1.51 log cfu/ml | blood -0.82 log cfu/ml |
| | 5 hrs: | peritoneum -1.51 log cfu/ml | blood -1.64 log cfu/ml |

All mice had only mild or no symptoms of infection (Table 2).

**Discussion and conclusion**

**[0176]** The purpose of this study was to investigate the efficacy of NZ17074 following intravenous (i.v.)

administration of a single dose of 7.5 mg/kg in the neutropenic peritonitis model in NMRI mice. A significant ($p< 0.001$) reduction of more the 3 $log_{10}$ CFU/ml compared to vehicle treatment was observed for NZ17074 in blood and peritoneal fluid at 5 hrs after treatment. Also at 2 hrs after treatment with NZ17074 a significant reduction ($p< 0.001$) both in the blood and peritoneal fluid was observed. Meropenem showed a significant reduction compared to the vehicle group ($p< 0.01$) both in the blood and in the peritoneal fluid at 5 hrs but at 2 hrs after treatment only in the peritoneal fluid.

**Table 5.** Colony counts of *E. coli* AID#172 in mice treated with a single dose of NZ17074, vehicle or meropenem

| Treatment | id no. | Time of sampling | Score | | | $log_{10}$ CFU | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | T=0h | T=2hrs | T=5hrs | PF | mean PF | Blood | Mean Blood |
| NZ17074 7.5 mg/kg | 4 | T = 5 | 0 | | 0 | 2.18 | 1.96 *** | 1.00 | 1.00 *** |
| | 5 | T = 5 | 0 | | 1 | 2.30 | | 1.00 | |
| | 6 | T = 5 | 0 | | 1 | 1.40 | | 1.00 | |
| Meropenem 40 mg/kg | 7 | T = 5 | 0 | | 0 | 4.38 | 4.21 ** | 3.20 | 3.10 ** |
| | 8 | T = 5 | 0 | | 0 | 4.00 | | 2.85 | |
| | 9 | T = 5 | 0 | | 0 | 4.26 | | 3.26 | |
| Vehicle | 10 | T = 5 | 0 | | 0 | 5.39 | 5.72 | 4.63 | 4.74 |
| | 11 | T = 5 | 0 | | 0 | 5.99 | | 5.24 | |
| | 12 | T = 5 | 0 | | 0 | 5.78 | | 4.36 | |
| NZ17074 7.5 mg/kg | 16 | T = 2 | 0 | 1 | | 4.24 | 3.79 ** | 2.04 | 2.08 ** |
| | 17 | T = 2 | 0 | 1 | | 3.60 | | 2.20 | |
| | 18 | T = 2 | 0 | 1 | | 3.54 | | 2.00 | |
| Meropenem 40 mg/kg | 19 | T = 2 | 0 | 1 | | 4.12 | 3.92 ** | 3.60 | 3.76 |
| | 20 | T = 2 | 0 | 1 | | 3.40 | | 3.57 | |
| | 21 | T = 2 | 0 | 1 | | 4.24 | | 4.11 | |
| Vehicle | 22 | T = 2 | 0 | 0 | | 4.89 | 5.43 | 3.21 | 4.58 |
| | 23 | T = 2 | 0 | 1 | | 5.65 | | 5.39 | |
| | 24 | T = 2 | 0 | 0 | | 5.74 | | 5.15 | |
| None | 25 | T = 2 | 0 | 0 | | 4.45 | 5.08 | 4.39 | 4.33 |
| | 26 | T = 2 | 0 | 0 | | 5.42 | | 4.57 | |
| | 27 | T = 2 | 0 | 0 | | 5.38 | | 4.02 | |
| None | 28 | T = 0 | 0 | | | 1.88 | 3.57 | 1.00 | 3.54 |
| | 29 | T = 0 | 0 | | | 3.71 | | 4.27 | |
| | 30 | T = 0 | 0 | | | 5.13 | | 5.35 | |

PF: peritoneal fluid. Used inoculum: $1.97 \times 10^6$ CFU/ml.
# Mouse received 0.35 ml instead of 0.30 ml of test compound
* $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared to vehicle group.

**EXAMPLE 4**

**Neutropenic thigh infection model: Efficacy of NZ17074 against *Escherichia coli* AID#172 and estimation of ED50**

**Introduction**

**[0177]** The purpose of this study was to investigate the dose-response relationship following intravenous (i.v.) administration of a single dose of NZ17074 ranging from 0.16 - 12 mg/kg. The effect was tested against *E. coli* AID#172 in the neutropenic thigh model. Treatment with 40 mg/kg meropenem was included as a positive control group. The colony counts in thighs were determined at 5 hrs after treatment.

**[0178]** The thigh infection model is a well-recognized model for studies of antimicrobial effect and tissue penetration as described by S. Gudmundsson & H. Erlensdottir: Handbook of Animal Models of Infection (1999), ed. by O. Zak & M. A. Sande, Academic Press, San Diego, US and in several publications. Reviewed by D. Andes & C. Craig: Animal model pharmacokinetics and pharmacodynamics: a critical review. International Journal of Antimicrobial Agents, 19(4): 261-268

**Materials and Methods**

**[0179]**

• 40 outbred, NMRI female mice, 25-30 gram (Harlan Scandinavia)

• *Escherichia. coli* AID#172 from Statens Serum Instute, Copenhagen, Denmark: Clinical isolate from a human wound from 2003. Multiresistant (Ampicillin, Ceftazidime, Aztreonam, Gentamicin, Ciprofloxacin)

• NZ17074 in Ringer Acetate, pH 6: 1.2 mg/ml, 6.0 ml. The solution was stored at 4°C until use. Analyses of the dose formulations used were performed after completion of the in-life phase of the study and gave the following results:

| Intended concentration | Measured concentration |
|---|---|
| 1.2 mg/ml | 1.11 mg/ml |
| 0.6 mg/ml | 0.51 mg/ml |
| 0.3 mg/ml | 0.24 mg/ml |
| 0.15 mg/ml | 0.14 mg/ml |
| 0.075 mg/ml | 0.043 mg/ml |
| 0.03 mg/ml | 0.010 mg/ml |
| 0.016 mg/ml | 0.002 mg/ml |

• Vehicle (Ringer Acetate pH 6). The solution was stored at 4°C until use

• Meronem®(AstraZeneca, 500 mg infusion substance, meropenem). Lot no. 09466C Date of expire: 08-2013

• Water, sterile

• 0.9% saline, sterile

• Sendoxan® (Cyclophosphamide, Baxter, 1 g) Batch nr. 0A671C Date of expire: 01-2013

• 5% Horse Blood Agar plates

• Lactose bromthymol blue agar plates

**Laboratory animal facilities and housing of mice**

**[0180]** The temperature and humidity were registered daily in the animal facilities. The temperature was 21 °C +/- 2°C and can be regulated by heating and cooling. The humidity was 55 +/- 10%. The air changes per hour were approximately 10-20 times, and light/dark period was in 12-hours interval of 6 a.m.- 6 p.m./6 p.m - 6 a.m.

**[0181]** The mice had free access to domestic quality drinking water and food (2016, Harlan). The mice were housed in Type 3 macrolone cages with 4 mice/cage. The bedding was Aspen Wood from Tapvei. Further the animals were offered paper strands from Sizzle-nest as nesting material. Mice were marked on the tail for individual identification within the cage. Mice were weighed the day before dosing

**Preparation of NZ17074 solutions**

**[0182]** The solution of 1.2 mg/ml was further diluted in PBS vehicle as follows:

| | |
|---|---|
| 0.6 mg/ml ~ 7.5 mg/kg: | 1.5 ml of 1.2 mg/ml NZ17074 + 1.5 ml vehicle |
| 0.3 mg/ml ~ 5.0 mg/kg: | 1.5 ml of 0.6 mg/ml NZ17074 + 1.5 ml vehicle |
| 0.15 mg/ml ~ 2.5 mg/kg: | 1.5 ml of 0.3 mg/ml NZ17074 + 1.5 ml vehicle |
| 0.075 mg/ml ~ 1.25 mg/kg: | 1.5 ml of 0.15 mg/ml NZ17074 +1.5 ml vehicle |
| 0.03 mg/ml ~ 0.63 mg/kg: | 1.5 ml of 0.075 mg/ml NZ17074 +2.25 ml vehicle |
| 0.016 mg/ml ~ 0.16 mg/kg: | 1.5 ml of 0.03 mg/ml NZ17074 +1.5 ml vehicle |

**Preparation meropenem solution**

**[0183]** Treatment with meropenem 40 mg/kg was included as a positive control group.

**[0184]** A total of 500 mg meropenem (one ampoule) was dissolved in 10 ml water ~ 50 mg/ml This stock solution was further diluted to 4 mg/ml (0.4 ml 50 mg/ml + 4.6 ml saline).

**Preparation of cyclophosphamide**

**[0185]** A total of 1 g cyclophosphamide (one ampoule Sendoxan® 1 g) was dissolved in 50 ml water ~ 20 mg/ml on each day of use. This stock solution was further diluted to 11 mg/ml (16.5 ml 20 mg/ml + 13.5 ml saline) for use on day -4 or to 5 mg/kg (8.25 ml 20 mg/ml + 21.75 ml saline)) for use on day -1.

**Treatment of mice with cyclophosphamide**

**[0186]** The mice were rendered neutropenic by injecting 0.5 ml cyclophosphamide solution intraperitoneally 4 days (200 mg/kg) and 1 day (100 mg/kg) prior to inoculation.

**Inoculation of mice**

**[0187]** Fresh overnight *E. coli* AID#172 colonies from a 5% Horse Blood Agar plate were suspended and diluted in sterile saline to approximately 2 x$10^7$ CFU/ml. One hour before start of treatment (time -1 hr) mice were inoculated intramuscularly with 0.05 ml of the *E. coli* suspension in the left hind leg. Approximately ½ hrs before inoculation mice were treated orally with 45 l neurophen (20 mg ibuprofen/ml corresponding to 30 mg/kg) as a pain relief.

**Treatment of mice**

**[0188]** The mice were treated i.v. in the lateral tail vein over approximately 30 seconds with 10 ml/kg with a single dose of NZ17074, meropenem or vehicle at time 0 hr (see Table 1). The dosing was based on a mean weight of 30 g. Mice that weighed 28-32 g received 0.30 ml solution. Mice that weighed 27-28 g received 0.25 ml solution and mice that weighed 32.1-36 g received 0.35 ml solution.

**Table 6. Treatment and sampling schedule in the murine thigh model.**

| Inoculation i.m. at - 1 hr | Intravenous treatment at 0 hr | Sampling and mouse no. | |
|---|---|---|---|
| | | 0 hr | 5 hrs |
| 0.05 ml of *E. coli* AID# 172 2x$10^7$ CFU/ml | Vehicle, Ringer acetate | | 1-2-3-4 |
| | NZ17074 0.16 mg/kg | | **5-6-7-8** |
| | NZ17074 0.30 mg/kg | | **9-10-11-12** |
| | NZ17074 0.75 mg/kg | | **13-14-15-16** |
| | NZ17074 1.5 mg/kg | | **17-18-19-20** |
| | NZ17074 3.0 mg/kg | | **21-22-23-24** |
| | NZ 17074 6.0 mg/kg | | **25-26-27-28** |
| | NZ17074 12 mg/kg | | **29-30-31-32** |
| | meropenem 40 mg/kg | | **33-34-35-36** |
| | No treatment | **37-38-39-40** | |
| T indicates the time in relation to treatment. Numbers in the sampling columns are mouse identification numbers. | | | |

**Clinical Scoring of mice**

**[0189]** The mice were observed during the study and scored 0-5 based on their behaviour and clinical signs.

| | |
|---|---|
| Score 0: | Healthy. |
| Score 1: | Minor clinical signs of infection and inflammation e.g. observations of minor signs of distress or changed activity. |
| Score 2: | Clear signs of infection like, social withdrawal, lack of curiosity, changed body position, piloerection, or changes in pattern of movement. |
| Score 3: | Severe signs of infection like stiff movements, lack of curiosity, changed body |

| | |
|---|---|
| | position, piloerection, pain, or changes in pattern of movement. |
| Score 4: | Severe pain and the mouse was sacrificed immediately to minimize the suffering of the animal. |
| Score 5: | The mouse was dead. |

**Sampling**

**[0190]** Colony counts were determined from thighs at 0 and 5 hrs. The mice were anaesthetized with $CO_2$ + $O_2$ and sacrificed. Immediately after, skin was removed and the left hind leg was collected and frozen at -70°C. After thawing, the thighs were homogenized using a Dispomix® Drive. Each sample was then 10 fold diluted in saline and 20-µl spots were applied on blue agar plates. All agar plates were incubated 18-22 hrs at 35°C in ambient air.

**Results**

**[0191]** The colony counts were performed at the start of treatment and 5 hrs after treatment. The CFU counts are shown in Table 3. The CFU numbers are $\log_{10}$ transformed before performing calculations.

**[0192]** The CFU/ml in the inoculum was determined to 7.35 $\log_{10}$ corresponding to 6.05$\log_{10}$ CFU/mouse. The high variability observed may be caused by suboptimal inoculation of some mice and resulting in too low CFU values. The lowest value in each group was therefore excluded from graphs and calculations (se table 3). At start of treatment the mean $\log_{10}$ CFU/ml was 4.93 and increased to 6.49 $\log_{10}$ CFU/ml in the vehicle group at 5 hrs after treatment. Slightly lower CFU levels were observed after treatment with NZ17074 0.16-3.0 mg/kg. Significantly lower CFU levels were observed after treatment with 6 mg/kg ($p<0.05$) and 12 mg/kg ($p<0.01$) NZ17074 compared to vehicle treatment (Table 3). Meropenem treatment, 40 mg/kg, resulted in slight but not significant reduction compared to the vehicle treated mice.

**[0193]** The dose-response curves (not shown) were calculated in GraphPad Prism using Sigmoidal dose-response (variable slope). From this the ED50 value was determined to 5.9 mg/kg. However, a bottom plateau was not obtained and this value may therefore be underestimated.

**[0194]** The maximum effect of NZ17074, $E_{max}$, was defined as the log CFU difference between no response and maximum response. No response was characterised as colony counts at the same level as determined for vehicle treated mice. The $E_{max}$ was calculated as the difference between the "Top plateau" and "Bottom plateau" in GraphPad Prism using Sigmoidal dose-response to be 2.4 $\log_{10}$ CFU/ml. In addition the 1 log killing, defined as the dose required to obtain 1 log reduction in bacterial loads compared to start of treatment, was estimated using GraphPad Prism to 6.1 mg/kg. A 2 and 3 log killing was not obtained

**[0195]** No clinical signs of infection were observed at any time point in any of the mice.

**Table 7.** Efficacy values for NZ17074 against *E. coli* AID#172 calculated in Graph Pad Prism

| | |
|---|---|
| TOP | 1.1 $\Delta\log_{10}$ CFU/ml |
| BOTTOM | -1.3 $\Delta\log_{10}$ CFU/ml |

| | |
|---|---|
| Emax | 2.4 $\Delta log_{10}$ CFU/ml |
| ED50 | 5.9 mg/kg |
| $R^2$ | 0.46 |
| 1 log killing | 6.1 mg/kg |

**Table 8.** Colony counts of *E. coli* AID#172 in thighs from neutropenic mice treated with a single dose of NZ17074, meropenem or vehicle.

| Treatment T = 0 hrs | mouse no. | Time of sampling | $log_{10}$ CFU thigh | mean | Treatment T = 0 hrs | mouse no. | Time of sampling | $log_{10}$ CFU thigh | mean |
|---|---|---|---|---|---|---|---|---|---|
| Vehicle | 1 | T = 5 | 5.16¤ | 6.49 | NZ17074 3.0 mg/kg | 21 | T = 5 | 5.30 | 6.07 |
| | 2 | T = 5 | 6.47 | | | 22 | T = 5 | 6.03 | |
| | 3 | T = 5 | 6.13 | | | 23 | T = 5 | 4.85¤ | |
| | 4 | T = 5 | 6.86 | | | 24 | T = 5 | 6.89 | |
| NZ17074 0.16 mg/kg | 5 | T = 5 | 3.18¤ | 5.16 | NZ17074 6.0 mg/kg | 25 | T = 5 | 2.75 | 4.10 * |
| | 6 | T = 5 | 6.03 | | | 26 | T = 5 | 4.54 | |
| | 7 | T = 5 | 3.30 | | | 27 | T = 5 | 1.48¤ | |
| | 8 | T = 5 | 6.15 | | | 28 | T = 5 | 5.01 | |
| NZ17074 0.30 mg/kg | 9 | T = 5 | 2.00¤ | 5.09 | NZ17074 12 mg/kg | 29 | T = 5 | 2.48¤ | 3.32 ** |
| | 10 | T = 5 | 5.40 | | | 30 | T = 5 | 3.27 | |
| | 11 | T = 5 | 3.10 | | | 31 | T = 5 | 3.19 | |
| | 12 | T = 5 | 6.78 | | | 32 | T = 5 | 3.51 | |
| NZ17074 0.75 mg/kg | 13 | T = 5 | 2.9¤ | 6.33 | Meropenem 40 mg/kg | 33 | T = 5 | 3.08¤ | 4.25 |
| | 14 | T = 5 | 5.72 | | | 34 | T = 5 | 3.81 | |
| | 15 | T = 5 | 7.27 | | | 35 | T = 5 | 4.99 | |
| | 16 | T = 5 | 6.00 | | | 36 | T = 5 | 3.94 | |
| NZ17074 1.5 mg/kg | 17 | T = 5 | 2.56¤ | 5.62 | None | 37 | T = 0 | 4.98 | 4.93 |
| | 18 | T = 5 | 6.23 | | | 38 | T = 0 | 3.81¤ | |
| | 19 | T = 5 | 4.93 | | | 39 | T = 0 | 4.79 | |
| | 20 | T = 5 | 5.70 | | | 40 | T = 0 | 5.01 | |

¤ This value was excluded from calculations as it was considered an outlier.
Stars indicate significantly different from vehicle group (Annova; multiple comparison).
* corresponds to $p<0.05$; ** corresponds to $p<0.01$.
Detection limit 1.4 $log_{10}$ CFU/ml.

**SEQUENCE LISTING**

**[0196]**

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Tyr Arg Arg Cys Asn
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Cys Arg Arg Cys Asn
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<210> 93
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Tyr Arg Arg Cys Asn
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<210> 95
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His Arg Arg Cys Asn
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His Arg Arg Cys Asn
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His Arg Arg Cys Asn
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<210> 98
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<400> 98
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His Arg Arg Cys Asn
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<210> 99
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His Arg Arg Cys Asn
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<400> 102

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<223> Synthetic antimicrobial peptide

<400> 103

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His Arg Arg Cys Asn
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<400> 105

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His Arg Arg Cys Asn
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His Arg Arg Cys Asn
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His Arg Arg Cys Asn
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1 5 10 15

His Arg Arg Cys Asn
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His Arg Arg Cys Asn
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His Arg Arg Cys Asn
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His Arg Arg Cys Asn
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His Arg Arg Cys Asn
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His Arg Arg Cys Asn
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His Arg Arg Cys Asn
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His Arg Arg Cys Asn
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Tyr Arg Arg Cys Asn
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Tyr Arg Arg Cys Asn
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Tyr Arg Arg Cys Asn
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Gln Arg Arg Cys Asn
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1 5 10 15

His Arg Arg Cys Asn

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<400> 139
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1 5 10 15

Tyr Arg Arg Cys Lys
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1 5 10 15

Tyr Arg Arg Cys Leu
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1 5 10 15

Tyr Arg Arg Cys Met
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<400> 142
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1 5 10 15

Tyr Arg Arg Cys Pro
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Tyr Arg Arg Cys Arg
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Tyr Arg Arg Cys Asn
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<400> 149
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1 5 10 15

Tyr Arg Arg Cys Asn
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Tyr Arg Arg Cys Asn

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<400> 153
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1 5 10 15

Tyr Arg Arg Cys Asn
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<400> 154
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1 5 10 15

Tyr Arg Arg Cys Asn
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1 5 10 15

Tyr Arg Arg Cys Asn
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<400> 156
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1 5 10 15

Tyr Arg Arg Cys Asn
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Tyr Arg Arg Cys Asn
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<210> 159

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Tyr Arg Arg Cys Asn
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Phe Arg Arg Cys Asn
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Gly Arg Arg Cys Asn
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1 5 10 15

Ile Arg Arg Cys Asn
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1 5 10 15

Leu Arg Arg Cys Asn
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1 5 10 15

Thr Arg Arg Cys Asn
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1 5 10 15

Val Arg Arg Cys Asn
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1 5 10 15

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Tyr Arg Arg Cys Asn
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1 5 10 15

Tyr Arg Arg Cys Asn
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<400> 176
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Tyr Arg Arg Cys Asn
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Tyr Arg Arg Cys Asn
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Tyr Arg Arg Cys Asn
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Tyr Arg Arg Cys Asn
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Tyr Arg Arg Cys Asn
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Ser Arg Arg Cys Asn
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<211> 21

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<213> Artificial

<220>

<223> Synthetic antimicrobial peptide

<400> 546

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<223> Synthetic antimicrobial peptide

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Lys Arg Arg Cys Asn
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Lys Arg Arg Cys Asn
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# REFERENCES CITED IN THE DESCRIPTION

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# krav

1. Isoleret antimikrobielt peptid omfattende aminosyresekvensen valgt fra gruppen bestående af SEQ ID NO: 72 og SEQ ID NO: 350.

2. Isoleret polynukleotid kodende for peptidet ifølge krav 1.

3. Nukleinsyrekonstruktion omfattende polynukleotidet ifølge krav 2.

4. Ekspressionsvektor omfattende polynukleotidet ifølge krav 2.

5. Værtscelle omfattende polynukleotidet ifølge krav 2.

6. Fremgangsmåde til fremstilling af et antimikrobielt peptid ifølge krav 1, omfattende:
a) dyrkning af værtscellen ifølge krav 5 under betingelser egnede til ekspression af peptidet; og
b) udvinding af peptidet.

7. Peptid ifølge krav 1 til anvendelse som et medikament.

8. Peptid ifølge krav 1 til anvendelse ved fremstillingen af et medikament til behandling af en mikrobiel infektion.