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AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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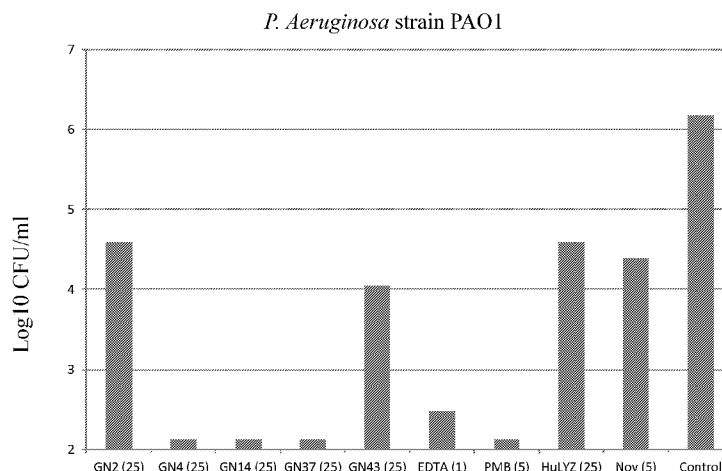
- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report:

1 June 2017

(54) Title: LYSIN POLYPEPTIDES ACTIVE AGAINST GRAM-NEGATIVE BACTERIA

FIGURE 4.



(57) Abstract: The present disclosure provides methods and compositions useful for the prophylactic and therapeutic amelioration and treatment of infections caused by Gram-negative bacteria, including *Pseudomonas aeruginosa*. The disclosure further provides compositions and methods of incorporating and utilizing lysin polypeptides of the present disclosure for augmenting the efficacy of antibiotics generally suitable for the treatment of Gram-negative bacterial infection.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/052338

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a. ☐ forming part of the international application as filed:
- ☐ in the form of an Annex C/ST.25 text file.
- ☐ on paper or in the form of an image file.
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- c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
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2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/052338

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-24(partially)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/052338

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/16 A61K38/46 A61P31/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, INSPEC, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Y. BRIERS ET AL: "Use of bacteriophage endolysin EL188 and outer membrane permeabilizers against <i>Pseudomonas aeruginosa</i> ", JOURNAL OF APPLIED MICROBIOLOGY., vol. 110, no. 3, 17 January 2011 (2011-01-17), pages 778-785, XP55330833, GB ISSN: 1364-5072, DOI: 10.1111/j.1365-2672.2010.04931.x the whole document abstract ----- -/--	1-24



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 March 2017

Date of mailing of the international search report

21/04/2017

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/052338

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MORITA M ET AL: "Functional analysis of antibacterial activity of Bacillus amyloliquefaciens phage endolysin against Gram-negative bacteria", FEBS LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 500, no. 1-2, 29 June 2001 (2001-06-29), pages 56-59, XP004251377, ISSN: 0014-5793, DOI: 10.1016/S0014-5793(01)02587-X the whole document paragraph [02.4]; figures; tables -----	1-24
A	ANDREU D: "Identification of an anti-mycobacterial domain in NK-lysin and granulysin", BIOCHEMICAL JOURNAL, PORTLAND PRESS LTD, GB, vol. 344, 1 January 1999 (1999-01-01), pages 845-849, XP002986058, ISSN: 0264-6021, DOI: 10.1042/0264-6021:3440845 the whole document page 848, left-hand column; table 1 -----	1-24
X	US 2014/094401 A1 (FARRIS MICHAEL HEATH [US]) 3 April 2014 (2014-04-03) cited in the application -----	1,24
Y	the whole document claims; figures; examples -----	1-16, 18-24
X	M.H. FARRIS ET AL: "Mitrecin A, an endolysin-like bacteriolytic enzyme from a newly isolated soil streptomycete", LETTERS IN APPLIED MICROBIOLOGY, vol. 58, no. 5, 24 May 2014 (2014-05-24), pages 493-502, XP055331061, GB ISSN: 0266-8254, DOI: 10.1111/lam.12220 -----	1,24
Y	the whole document pages 495-496; figure 2 -----	1-16, 18-24
X	ZHANG WANG ET AL: "Genomic insights into an obligate epibiotic bacterial predator: Micavibrio aeruginosavorus ARL-13", BMC GENOMICS, BIOMED CENTRAL LTD, LONDON, UK, vol. 12, no. 1, 21 September 2011 (2011-09-21), page 453, XP021110010, ISSN: 1471-2164, DOI: 10.1186/1471-2164-12-453 -----	5,6,9
Y	the whole document Additional file 4.; compound GMV_542 -----	1-16, 18-24
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/052338

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	M. PASTAGIA ET AL: "Lysins: the arrival of pathogen-directed anti-infectives", JOURNAL OF MEDICAL MICROBIOLOGY., vol. 62, no. Pt 10, 1 October 2013 (2013-10-01), pages 1506-1516, XP055330831, GB ISSN: 0022-2615, DOI: 10.1099/jmm.0.061028-0 the whole document	1-24
A	P. LUKACIK ET AL: "Structural engineering of a phage lysin that targets Gram-negative pathogens", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 109, no. 25, 19 June 2012 (2012-06-19), pages 9857-9862, XP055330837, US ISSN: 0027-8424, DOI: 10.1073/pnas.1203472109 the whole document	1-24
A	PETRA LUKACIK ET AL: "Using a bacteriocin structure to engineer a phage lysin that targets Yersinia pestis", BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 38, no. 6, 1 December 2012 (2012-12-01), pages 4672-1506, XP055330838, GB ISSN: 0300-5127, DOI: 10.1086/315217 the whole document	1-24
Y	Anonymous: "putative endolysin [Pseudomonas phage PAJU2]", NCBI, 18 February 2009 (2009-02-18), XP055359505, Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/protein/Y_P_002284361.1 [retrieved on 2017-03-28] abstract	1-24
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/052338

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	UCHIYAMA J ET AL: "Characteristics of a novel Pseudomonas aeruginosa bacteriophage, PAJU2, which is genetically related to bacteriophage D3", VIRUS RESEARCH, AMSTERDAM, NL, vol. 139, no. 1, 1 January 2009 (2009-01-01), pages 131-134, XP025816719, ISSN: 0168-1702, DOI: 10.1016/J.VIRUSRES.2008.10.005 [retrieved on 2008-12-02] the whole document -----	1-24
A	WO 2014/124047 A1 (ACADEMIA SINICA; LIANG CHI MING [US]) 14 August 2014 (2014-08-14) the whole document claims; figures; examples; sequence 16 -----	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/052338

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014094401 A1	03-04-2014	US 2014094401 A1	03-04-2014
		US 2016032349 A1	04-02-2016

WO 2014124047 A1	14-08-2014	CN 105101796 A	25-11-2015
		EP 2986115 A1	24-02-2016
		TW 201434855 A	16-09-2014
		US 2016002300 A1	07-01-2016
		WO 2014124047 A1	14-08-2014

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-24(partially)

A pharmaceutical composition according to claim 1, wherein the polypeptide corresponds to SEQ ID NO: 1. Vectors comprising nucleic acid encoding it according to claims 5, 6 and 9, as well as a host cell comprising said vector according to claim 7. Methods of treating bacterial infections caused by Gram negative bacteria, in particular *Pseudomonas Aeruginosa*, according to claims 11, 12, 17 and 18, as well as methods for augmenting the efficacy of an anti-Gram negative antibiotic by co-administering said polypeptide.

2. claims: 1-24(partially)

A pharmaceutical composition according to claim 1, wherein the polypeptide corresponds to SEQ ID NO: 2. Vectors comprising nucleic acid encoding it according to claims 5, 6 and 9, as well as a host cell comprising said vector according to claim 7. Methods of treating bacterial infections caused by Gram negative bacteria, in particular *Pseudomonas Aeruginosa*, according to claims 11, 12, 17 and 18, as well as methods for augmenting the efficacy of an anti-Gram negative antibiotic by co-administering said polypeptide.

3. claims: 1-24(partially)

A pharmaceutical composition according to claim 1, wherein the polypeptide corresponds to SEQ ID NO: 3 and 6-10. Vectors comprising nucleic acid encoding them according to claims 5, 6 and 9, as well as a host cell comprising said vector according to claim 7. Methods of treating bacterial infections caused by Gram negative bacteria, in particular *Pseudomonas Aeruginosa*, according to claims 11, 12, 17 and 18, as well as methods for augmenting the efficacy of an anti-Gram negative antibiotic by co-administering said polypeptides.

4. claims: 1-24(partially)

A pharmaceutical composition according to claim 1, wherein the polypeptide corresponds to SEQ ID NO: 4. Vectors comprising nucleic acid encoding it according to claims 5, 6 and 9, as well as a host cell comprising said vector according to claim 7. Methods of treating bacterial infections caused by Gram negative bacteria, in particular *Pseudomonas Aeruginosa*, according to claims 11, 12, 17 and 18, as well as methods for augmenting the efficacy of an

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

anti-Gram negative antibiotic by co-administering said polypeptide.

5. claims: 1-24(partially)

A pharmaceutical composition according to claim 1, wherein the polypeptide corresponds to SEQ ID NO: 5. Vectors comprising nucleic acid encoding it according to claims 5, 6 and 9, as well as a host cell comprising said vector according to claim 7. Methods of treating bacterial infections caused by Gram negative bacteria, in particular *Pseudomonas Aeruginosa*, according to claims 11, 12, 17 and 18, as well as methods for augmenting the efficacy of an anti-Gram negative antibiotic by co-administering said polypeptide.
