

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2018/064029

International filing date (day/month/year)
05.12.2018

Priority date (day/month/year)
07.12.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/78 C07K14/435 C12N15/82

Applicant
ZOETIS SERVICES LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established 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.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
 - ☒ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☒ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ 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.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>3-20, 22-42</u>
	No: Claims	<u>1, 2, 21, 43-49</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-49</u>
Industrial applicability (IA)	Yes: Claims	<u>1-49</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application is directed to a library of peptides derived from Tachyplesin, an antimicrobial *peptide* isolated from the Japanese horseshoe crab as early as 1988 (D3). The application attempts to describe variants of said Tachyplesin peptide by defining a least 13 amino acid substitutions out of a total of 17 amino acid residues of Wildtype Tachyplesin, i.e. 76% of the original peptide sequence changed. Moreover, the application attempts to exclude certain sequences by defining a number of provisions. However said provisions, or in other words disclaimers, do not exclude prior art from assessing inventive step.

It is obvious, that the present applications heavily depends on the outcome of tests carried out on certain Tachyplesin variants disclosed in the application. To this end, about 100 peptides variants have been tested, some of them show antibacterial activity, some improved safety characteristics, some show both. However, the scope of - in particular - claim 1 goes far beyond the tested examples.

- D1 WO 2016/026354 A1 (TIANJIN LANRY BIO TECHNOLOGY CO LTD [CN]) 25 February 2016 (2016-02-25)
- D2 CN 104 988 170 A (UNIV JILIN AGRICULTURAL) 21 October 2015 (2015-10-21)
- D3 Takanori Nakamura ET AL: "THE JOURNAL OF BIOLOGICAL CHEMISTRY by The American Society for Biochemistry and Molecular Biology, Inc. Printed in Tachyplesin, a Class of Antimicrobial Peptide from the Hemocytes of the Horseshoe Crab (*Tachyplesus tridentatus*) ISOLATION AND CHEMICAL STRUCTURE* NHZ-K-W-C-F-R-V-C-Y-R-G-I-C-Y-R-R-C-R",
, 1 January 1988 (1988-01-01), pages 16709-16713, XP055569178,
Retrieved from the Internet:
URL:<http://www.jbc.org/content/263/32/16709.full.pdf>

D1 discloses tachyplesin-antibody fusion proteins and preparation method thereof. The fusion protein comprises at least one tachyplesin unit, and the gene of a coded tachyplesin unit is directly connected to the 3' end or 5' end of a gene of a light chain or a coded antibody heavy chain. D1 is cited as an exemplary document, that the scope of the present set of claims is far too broad and covers a multitude of amino acid

sequences comprising the degenerated sequence as shown in claim 1 and more, particularly, sequences derived therefrom such as the peptide sequence with Seq-ID-N°31 of claim 21. In D1, the query sequence SEQ ID NO:31 has 100.00 % identity (100.00 % similarity) over 16 positions in a common overlap (range (q:s): 2-17:3-18) with subject GSP:BBU99642 (length: 18) from CN104177502-A published on 2014-12-03. The query sequence SEQ ID NO:30 has 100.00 % identity (100.00 % similarity) over 16 positions in a common overlap (range (q:s): 2-17:3-18) with subject GSP:BBU99642 (length: 18) from CN104177502-A published on 2014-12-03.

D1 thus anticipates the subject matter of present claims 1, 21 and 43-49 (Art.33(2) PCT. The provision of the subject matter of claims 2-20 and 22-42 does not involve an inventive activity as required by Art.33(3) PCT. In particular the specific definition of specific mutations as defined in claims 2-20 because they are not linked to any specific technical effect, neither does the application provide for any credible data suitable to prove a technical effect. In the absence of a credible effect for any of the claimed sequence variants, the objective technical problem can only be defined as the provision of just another Tachypleisin peptide, for which no inventive skill is necessary.

In order for an inventive step to be acknowledged for the whole of the current application it needs to be credible that the desired effect is present for the whole scope of the current application. Given the nature of some of the substituents in the present claims, in particular in claim 1, this is not the case. Besides the 10^{20} different possibilities to exchange amino acid compositions and therefore to alter the structure of the claimed peptide, further, e.g. chemical modification, fall under the scope of the present set of claims. Those vast variety of modifications cannot be regarded as obvious equivalents or modifications (plausible generalisation) of the tested examples. Accordingly said expressions should be restricted in this respect to the particular meanings specified in the description.

Similar to as D1, document D2 also discloses peptides and fusion peptides covered by the scope of the present set of claims. D2 discloses fusion antibacterial peptide and its preparation method and application. In particular, D2 discloses the king crab element antibacterial peptide tachypleisin I (TP I), a series of fusion constructs the optimisation of the disclosed cecropin antimicrobial peptides CB gene and the king crab element antibacterial peptide TP I gene. D2 discloses that the fusion antibacterial peptides show increased antibacterial activity and that there are no drug resistance problems.

In D2, the query sequence SEQ ID NO:28 has 100 % identity (100 % similarity) over 18 positions in a common overlap (range (q:s): 1-18:40-57) with subject GSP:BCN22561 (length: 64) from CN104988170-A published on 2015-10-21.

Consequently, D2 anticipates the subject matter of present claims 1, 21 and 43-49 (Art.33(2) PCT).

Re Item VIII

Certain observations on the international application

The Applicant is informed that, the present application will face substantive non-unity objections in the further proceedings of the application. In the present stage, it does, however, be appropriate nor feasible to subdivide the claimed peptides into different groups of invention. However, it is clear, that the overall concept of providing Tachyplesin variants is neither novel nor inventive (see D1-D3). In the absence of a common novel and inventive structural and/or functional feature, the provision of each and every Tachyplesin variant forms its own invention (Rule 13.1/2 PCT).

In case present application is pursued as European patent application claims 34-42 would not be patentable relating to a method of treatment of a subject. Claims 34-42 are directed towards therapeutic methods for the treatment of the human or animal body. Said claims therefore relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). Patentability, in particular novelty and inventive step, of said claims has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Present set of claims, in particular claim 1, must be interpreted as two-step-product-by-process claims wherein the result of the first step of the production method steers the development of the second step of the process. Even though the claim is written as a mere product claim, said product can also be made available by a tedious mutation and production process. In fact, the claim covers so many peptide variants, that the skilled person will never be capable to produce all of them, thus never be in position to test them all for a desired property. The skilled person thus has to rely on an element of chance to produce a desired peptide, a requirement that collides significantly with the requirements of Art.5 PCT.

The present set of claims is objected to under Art.6 PCT, because the claimed amino acid sequences are not clearly defined. In the absence of a functional limitation of the sequence variants, the claims lack clarity.