PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Drew Hissong
Wenderoth, Lind & Ponack LLP
1030 15th Street NW
Suite 400 East
Washington, District of Columbia 20005
United States of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	24 MAR 2017

Applicant's or agent's file reference	FOR FURTHER ACTION
2015-1549A	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US15/00313	23 December 2015 (23.12.2015)	23 December 2014 (23.12.2014)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 39/00, 38/16, 38/17; C12P 21/02; C07K 14/435 (2017.01)
CPC - A61K 38/1735, 38/1703, 38/1709, 38/02, 39/00; C07K 14/4727, 14/435

Applicant UNIVERSITY OF MARYLAND, BALTIMORE

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 43*bis*.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 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 66.1 *bis*(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/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	21 February 2017 (21.02.2017)	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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Box No. I Basis of this 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 43*bis*.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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5-11, 15, 19

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 5-11, 15, 19 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims Nos. 5-11, 15, and 19 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4 (a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 5-11, 15, 19

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, Claims 1-4 and 20-22 are directed toward a decoy peptide and method of treating or preventing a bacterial infection in a subject therewith.

Group II, Claims 12-14, 16-18 are directed toward methods of determining whether a subject has an infection, or has been colonized, by a selected bacteria.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include SEQ ID NO: 1, not present in Group II; the special technical features of Group II include detection of a shed MUC1 ectodomain, not present in Group I.
Groups I and II share the technical features including: a method, wherein a subject has an infection of a selected bacteria; and a MUC1 fragment.

However, these shared technical features are previously disclosed by the article 'Muc1 Limits Helicobacter felis Binding to Gastric Epithelial Cells but Does not Limit Colonization and Gastric Pathology Following Infection' by Every et al. (hereinafter 'Every').

Every discloses a method, wherein a subject has an infection of a selected bacteria (detection of a releasable MUC1 decoy by gastric epithelial cells upon infection with H. pylori (a method, wherein a subject has an infection of a selected bacteria); page 489, first column, first paragraph); and a MUC1 fragment (a releasable MUC1 decoy (a MUC1 fragment); page 489, first column, first paragraph).

Since none of the special technical features of the Groups I and II inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Every reference, unity of invention is lacking.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-4 and 20-22

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

1. Statement

Novelty (N)	Claims	1-2, 3/1-2, 4/1-2, 21, 22/20-21	YES
	Claims	20	NO
Inventive step (IS)	Claims	2, 3/2, 4/2, 21, 22/21	YES
	Claims	1, 3/1, 4/1, 20, 20/22	NO
Industrial applicability (IA)	Claims	1-2, 3/1-2, 4/1-2, 20-21, 22/20-21	YES
	Claims	NONE	NO

2. Citations and explanations:

Claim 20 lacks novelty under PCT Article 33(2) as being anticipated by WO 2004/033667 A2 (DEPARTMENT OF VETERANS AFFAIRS, REHABILITATION R & D SERVICE) (hereinafter 'DVA').

As per claim 20, DVA discloses a MUC1 decoy peptide (MUC1 peptide; page 29, lines 14-18) selected from the group consisting of: (a) a single repeat MUC I decoy peptide comprising at least 15 contiguous amino acids of GSTAPPAHGVTSAPDTRPAP (SEQ ID NO: 1) (SEQ ID NO: 1 of the instant PCT application is 100% identical to SEQ ID NO: 2 of the DVA reference, identified as a MUC1 peptide; page 29, lines 17-18), (b) a tandem-repeat MUC1 decoy peptide comprising at least five MUC1 repeats, wherein each MUC 1 repeat comprises at least 15 contiguous amino acids of (SEQ ID NO: I) and wherein the sequence of each MUC1 repeat may vary in the peptide, (c) an ectodomain MUC1 decoy peptide comprising the amino acid sequence (SEQ ID N0:2), wherein X is at least five MUC1 repeats, wherein each MUCI repeat comprises at least 15 contiguous amino acids of (SEQ ID NO: 1) and wherein the sequence of each MUC1 repeat may vary in the peptide, (d) a sequence variant MUCI decoy peptide having at least 80% sequence identity to a peptide of (a), (b) or (c), (e) a desialylated version of a peptide of (a), (b), (c) or (d), and (f) a deglycosylated version of a peptide of (a), (b), (c) or (d).

Claim 22/20 lacks an inventive step under PCT Article 33(3) as being obvious over DVA.

As per claim 22/20, DVA discloses a formulation comprising one or more MUC1 decoy peptides of Claim 20 and a carrier or diluent (the peptide in a cell-free preparation, which would intrinsically require a carrier or diluent; page 24, lines 15-18). DVA a pharmaceutical formulation comprising one or more MUC1 decoy peptides, and a pharmaceutically acceptable carrier or diluent. However, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the formulation comprising one or more MUC1 decoy peptides, as previously disclosed by DVA, to include a pharmaceutical formulation comprising a pharmaceutically acceptable carrier or diluent, in order to provide a safe means of administering the peptide to a subject as desired.

Claims 1, 3/1, and 4/1 lack an inventive step under PCT Article 33(3) as being obvious over the publication entitled 'MUC1 cell surface mucin is a critical element of the mucosal barrier to infection' by McAuley, et al. (hereinafter 'McAuley') in view of DVA.

As per claim 1, McAuley discloses a method of treating or preventing a bacterial infection in a subject (decoy mucin peptides for prevention of bacterial infections in the gut; page 2313, 2nd column, 2nd paragraph), comprising administering a therapeutically effective amount of one or more MUCI decoy peptides to a subject in need thereof (transfecting cells with MUC1-expressing vectors in a cell model of infection; page 2317, 1st column, 3rd paragraph). However, McAuley does not disclose wherein the one or more MUC 1 decoy peptide is selected from the group consisting of: (a) a single repeat MUCI decoy peptide comprising at least 15 contiguous amino acids of (SEQ ID NO: 1, (b) a tandem repeat MUCI decoy peptide comprising at least five MUC1 repeats, wherein each MUC 1 repeat comprises at least 15 contiguous amino acids of (SEQ ID NO: 1) and wherein the sequence of each MUC1 repeat may vary in the peptide, (c) an ectodomain MUC1 decoy peptide comprising the amino acid sequence (SEQ ID NO: 2), wherein X is at least five MUC1 repeats, wherein each MUC1 repeat comprises at least 15 contiguous amino acids of (SEQ ID NO: 1) and wherein the sequence of each MUCI repeat may vary in the peptide, (d) a sequence variant MUC1 decoy peptide having at least 80% sequence identity to a peptide of (a), (b) or (c), (d) a desialylated version of a peptide of (a), (b), (c) or (d), and (e) a deglycosylated version of a peptide of (a), (b), (c) or (d). DVA discloses a MUC1 decoy peptide (MUC1 peptide; page 29, lines 14-18) consisting of (a) a single repeat MUC1 decoy peptide comprising at least 15 contiguous amino acids of GSTAPPAHGVTSAPDTRPAP (SEQ ID NO: 1) (SEQ ID NO: 1 of the instant PCT application is 100% identical to SEQ ID NO: 2 of the DVA reference, identified as a MUC1 peptide; page 29, lines 17-18). It would have been obvious to a person of ordinary skill in the art, at the time of invention, to have modified the previous disclosure of McAuley to include a single repeat MUC1 decoy peptide comprising at least 15 contiguous amino acids of SEQ ID NO: 1, as previously disclosed by DVA, in order to provide an effective decoy peptide derived from the MUC1 protein.

As per claim 3/1, McAuley and DVA, in combination, disclose the method of claim 1, and McAuley further discloses wherein the bacterial infection is treated (Mucin decoy peptides limits mucosal infection by C. jejuni bacteria; page 2313, 2nd column, 2nd paragraph).

-***-Continued Within the Next Supplemental Box-***-

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Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claims 1 and 20 are objected to under PCT Rule 66.2(a) (iii) as containing the following defect(s) in the form or contents thereof: each of Claims 1 and 20 contains two items labeled (d). For the purposes of this examination, the assumption has been made that the second item (d) likely should have appeared as (e) and the item labeled (e) likely should have appeared as (f).

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

-***-Continued from Box V: Citations and Explanations-***-

As per claim 4/1, McAuley and DVA, in combination, disclose the method of claim 1, and McAuley further discloses wherein the bacterial infection is prevented (mucin decoy peptides result in intestinal cells having increased resistance to C. jejuni infection; page 2313, 2nd column, 2nd paragraph).

Claim 2 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of claim 1, wherein the MUC1 decoy peptide is the ectodomain MUC1 decoy peptide set forth in SEQ ID NO: 3, or a desialylated version thereof, or a deglycosylated version thereof.

McAuley discloses, in part, the method of Claim 1, but McAuley does not disclose wherein the MUCJ decoy peptide is the ectodomain MUCl decoy peptide set forth in SEQ ID NO: 3, or a desialylated version thereof, or a deglycosylated version thereof.

DVA discloses a MUC1 decoy peptide or a desialylated version thereof (page 27, lines 17-20). DVA does not disclose wherein the MUC1 decoy peptide is the ectodomain MUC1 decoy peptide set forth in SEQ ID NO: 3, or a desialylated version thereof, or a deglycosylated version thereof.

WO 2013/025972 A1 (GLOBEIMMUNE, INC., et al.) (hereinafter 'Globeimmune') discloses a peptide 87% identical to SEQ ID NO: 3 (SEQ ID NO: 3 of the instant PCT application is 87% identical to SEQ ID NO: 11 of the Globeimmune reference, identified as the human MUC1 protein sequence; paragraph [0066]). Globeimmune does not disclose wherein the MUC1 decoy peptide is the ectodomain MUC1 decoy peptide set forth in SEQ ID NO: 3, or a desialylated version thereof, or a deglycosylated version thereof.

US 2004/0157278 A1 to Astle, et al. (hereinafter 'Astle') discloses a peptide 87% identical to SEQ ID NO: 3 (SEQ ID NO: 3 of the instant PCT application is 87% identical to SEQ ID NO: 120 of the Astle reference, identified as the human MUC1 protein sequence; paragraph [0008]; Claim 7). Astle not disclose wherein the MUC1 decoy peptide is the ectodomain MUC1 decoy peptide set forth in SEQ ID NO: 3, or a desialylated version thereof, or a deglycosylated version thereof.

Thus, the prior art does not teach or fairly suggest the method of claim 1, wherein the MUC1 decoy peptide is the ectodomain MUC1 decoy peptide set forth in SEQ ID NO: 3, or a desialylated version thereof, or a deglycosylated version thereof, and sufficient motivation, based upon the previous disclosures of the McAuley, DVA, Globeimmune, and Astle references, does not exist to have determined and implemented the method as described in claim 2 of the instant PCT application.

Claims 3/2 and 4/2 meet the criteria set-out in PCT Article 33(2)-(3), due to their dependency upon positive Claim 2.

Claim 21 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the MUC1 decoy peptide of claim 20, wherein the MUC1 decoy peptide is the ectodomain MUC1 decoy peptide set forth in SEQ ID NO: 3, or a desialylated version thereof, or a deglycosylated version thereof.

DVA discloses the MUC1 decoy peptide of claim 20, or a desialylated version thereof (page 27, lines 17-20). DVA does not disclose wherein the MUC1 decoy peptide is the ectodomain MUC1 decoy peptide set forth in SEQ ID NO: 3, or a desialylated version thereof, or a deglycosylated version thereof.

Globeimmune discloses a peptide 87% identical to SEQ ID NO: 3 (SEQ ID NO: 3 of the instant PCT application is 87% identical to SEQ ID NO: 11 of the Globeimmune reference, identified as the human MUC1 protein sequence; paragraph [0066]). Globeimmune does not disclose wherein the MUC1 decoy peptide is the ectodomain MUC1 decoy peptide set forth in SEQ ID NO: 3, or a desialylated version thereof, or a deglycosylated version thereof.

Astle discloses a peptide 87% identical to SEQ ID NO: 3 (SEQ ID NO: 3 of the instant PCT application is 87% identical to SEQ ID NO: 120 of the Astle reference, identified as the human MUC1 protein sequence; Claim 7, paragraph [0008]). Astle not disclose wherein the MUC1 decoy peptide is the ectodomain MUC1 decoy peptide set forth in SEQ ID NO: 3, or a desialylated version thereof, or a deglycosylated version thereof.

Thus, the prior art does not teach or fairly suggest the MUC1 decoy peptide of claim 20, wherein the MUC1 decoy peptide is the ectodomain MUC1 decoy peptide set forth in SEQ ID NO: 3, or a desialylated version thereof, or a deglycosylated version thereof, and sufficient motivation, based upon the previous disclosures of the DVA, Globeimmune, and Astle references, does not exist to have determined and implemented the MUC1 decoy peptide as described in claim 21 of the instant PCT application.

Claim 22/21 meets the criteria set-out in PCT Article 33(2)-(3), due to its dependency upon positive Claim 21.

Claims 1-2, 3/1-2, 4/1-2, 20-21, and 22/20-21 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.