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14/650,767	06/09/2015	Hikaru MIZUMURA	Q220395	1531
23373 7590 09/16/2016 SUGHRUE MION, PLLC 2100 PENNSYLVANIA AVENUE, N.W. SUITE 800 WASHINGTON, DC 20037			EXAMINER STEADMAN, DAVID J	
			ART UNIT 1656	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Office Action Summary	Application No. 14/650,767	Applicant(s) MIZUMURA ET AL.	
	Examiner DAVID J. STEADMAN	Art Unit 1656	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 08/24/2016.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 43-64 is/are pending in the application.
5a) Of the above claim(s) 51-53, 58-61 and 64 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☒ Claim(s) 43-50, 54-57, 62 and 63 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☒ The specification is objected to by the Examiner.

11) ☒ The drawing(s) filed on 06/09/2015 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☒ All b) ☐ Some** c) ☐ None of the:

1. ☒ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.

4) ☒ Other: Appendix A.

DETAILED ACTION

Status of the Application

1. The present application is being examined under the pre-AIA first to invent provisions.
2. Claims 43-64 are pending in the application.

Election/Restriction

3. Applicant's election without traverse of Group I, claims 43-50, 54-57, 62, and 63, and the species SEQ ID NO: 2 in the reply filed on 8/24/2016 is acknowledged.

Claims 51-53, 58-61, and 64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 8/24/2016.

Claims 43-50, 54-57, 62, and 63 are being examined on the merits with claim 49 being examined only to the extent the claim reads on the elected subject matter.

It is noted that claims 54, 62, and 63 depend from non-elected claim 51 and it is suggested that claim 54 be re-written in independent form, longer being dependent from a non-elected claim.

Claim for Priority

4. This application is a 35 U.S.C. 371 national stage filing of PCT/JP2013/083082, filed on 12/10/2013, which claims foreign priority under 35 USC § 119(a)-(d) to

Japanese application 2012-269840, filed on 12/10/2012. A certified copy of the foreign priority document has been filed in this application on 6/9/2015.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 6/9/2015, 7/16/2015, 8/5/2015, and 8/3/2016 was filed prior to the mailing date of the instant first Office action on the merits. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

The IDS filed on 6/9/2015 and 7/16/2015 have been lined through because the cited references are duplicates to those cited in the IDS filed on 8/5/2015.

Specification/Informalities

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See specification at p. 78, paragraph 115. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code; references to websites should be limited to the top-level domain name without any prefix such as http:// or other browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 43-50, 54-57, 62, and 63 are rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP 2163.II.A.2.(a).i) states, "Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention". For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 further states that a "representative number of species" means that the species which are adequately described are representative of the entire

genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Claim 43 (claims 56 and 57 dependent therefrom) is drawn to a genus of horseshoe crab Factor C polypeptides having activity of Factor C. According to the specification, "the activity of Factor C refers to such an activity that the Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B" (spec at p. 36, paragraph 28).

Claim 44 is drawn to the Factor C according to claim 43, which is a recombinant protein. According to the specification, the term "recombinant protein" refers to a protein obtained through introduction of a gene encoding the protein into a host cell and heterologous expression of the gene (paragraph 19).

Claim 45 is drawn to the Factor C according to claim 43, which contains (α -2,3) linked terminal sialic acid.

Claim 46 is drawn to the Factor C according to claim 45, which contains (α -2,3) linked terminal sialic acid in a greater amount, as compared with a native Factor C and/or a horseshoe crab Factor C expressed in Sf9 as a host cell.

Claim 47 is drawn to the Factor C according to claim 43, which exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate.

Claim 48 is drawn to the Factor C according to claim 43, which has a molecular weight of 115 kDa to 140 kDa or a molecular weight of 127 kDa $\pm$ 5 kDa, as measured through SDS-PAGE under a non-reducing condition.

Claim 49 is drawn to (in relevant part) the Factor C according to claim 43, which is a protein shown in the following (A), (B), (C), or (D):

(A) a protein comprising the amino acid sequence shown in SEQ ID NO: 2; and

(B) a protein comprising the amino acid sequence shown in SEQ ID NO:2 but which includes substitution, deletion, insertion, or addition of one or several amino acid residues, and having activity of Factor C.

As noted above, according to the specification, "the activity of Factor C refers to such an activity that the Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B" (spec at p. 36, paragraph 28). The structure of the Factor C is unlimited.

Claim 50 is drawn to the Factor C according to claim 43, which is water-soluble.

Claim 54 (claims 62 and 63 dependent therefrom) is drawn to a horseshoe crab Factor C producible by a method comprising expressing the horseshoe crab Factor C in a mammalian cell as a host cell.

Claim 55 is drawn to the Factor C according to claim 43, which is producible by a method comprising expressing the horseshoe crab Factor C in a mammalian cell as a host cell.

In this case, the specification discloses an actual reduction to practice of the following representative species of the genus of claimed horseshoe crab Factor C polypeptides: Factor C isolated from *Tachypleus tridentatus* or *Carcinoscorpius rotundicauda* hemocyte lysate and *Tachypleus tridentatus* Factor C expressed in Sf9 insect cells, Chinese Hamster Ovary (CHO) cells, or human embryonic kidney (HEK)

cells, which Factor C polypeptides have Factor C activity. While one of skill in the art would expect a horseshoe crab Factor C polypeptide that is isolated from its natural source to have activity of Factor C, the specification supports a high level of unpredictability regarding the activity of a horseshoe crab Factor C that is recombinantly expressed in a heterologous host cell. For example, the specification discloses that a horseshoe crab Factor C that is recombinantly expressed in a *Drosophila* S2 cell does not have Factor C activity (paragraph 132). Also, regarding the terminal sialic acid, residual activity in the presence of sodium citrate, molecular weight, amino acid sequence, solubility, and expression in a mammalian cell, the specification supports a high level of unpredictability regarding the terminal sialic acid, residual activity in the presence of sodium citrate, molecular weight, amino acid sequence, solubility, and expression in a mammalian cell of a horseshoe crab Factor C that is recombinantly expressed. For example, regarding the terminal sialic acid, the specification discloses that a horseshoe crab Factor C that is recombinantly expressed in Sf9 cells does not have any (α -2,3) linked terminal sialic acid, while Factor C that is recombinantly expressed in CHO and HEK cells contains (α -2,3) linked terminal sialic acid (paragraph 154). Regarding residual activity in the presence of sodium citrate, Figure 7 shows that Factor C that is recombinantly expressed in Sf9 cells has almost no residual activity in the presence of 21 mM sodium citrate, Factor C that is recombinantly expressed in CHO and HEK cells retains about 25% residual activity in the presence of 21 mM sodium citrate. Regarding molecular weight, the specification discloses that a horseshoe crab Factor C that is recombinantly expressed in Sf9 cells has a molecular

weight of 109 kDa, while the same Factor C that is recombinantly expressed in CHO and HEK cells has a molecular weight of 128 or 124 kDa, respectively (Table 1). Regarding amino acid sequence, the specification fails to identify any alterations to the amino acid sequence of SEQ ID NO: 2 that can be made and still have the identity of a horseshoe crab Factor C polypeptide and as described above, the same horseshoe crab Factor C expressed in different host cells can have very different characteristics and even be non-functional. Regarding solubility, the specification discloses that a horseshoe crab Factor C that is recombinantly expressed in COS cells is insoluble (paragraph 11). In this case, the genus of claimed horseshoe crab Factor C polypeptides is widely variant, encompassing any horseshoe crab Factor C polypeptide expressed from any host cell and in view of the relative few disclosed representative species and the high level of unpredictability regarding the functionality, terminal sialic acid, residual activity in the presence of sodium citrate, molecular weight, amino acid sequence, and solubility, one of skill in the art would not accept the disclosure of Factor C isolated from *Tachypleus tridentatus* or *Carcinoscorpius rotundicauda* hemocyte lysate and *Tachypleus tridentatus* Factor C expressed in Sf9 insect cells, CHO cells, or HEK cells as being representative of all other horseshoe crab Factor C polypeptides as encompassed by the claims. As such, the specification, taken with the pre-existing knowledge in the art of amino acid substitution, fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

8. Claims 43-50, 54-57, 62, and 63 are rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for Factor C isolated from *Tachypleus tridentatus* or *Carcinoscorpius rotundicauda* hemocyte lysate and *Tachypleus tridentatus* Factor C expressed in Sf9 insect cells, CHO cells, or HEK cells, does not reasonably provide enablement for all horseshoe crab Factor C polypeptides as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

“The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.” *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors considered to be most relevant to the instant rejection are addressed in detail below.

The nature of the invention: According to the specification, “there has never been known a case where functional Factor C is produced using mammalian cells as host cells” (paragraph 11) and “[a]n object of the present invention is to provide a novel

recombinant horseshoe crab Factor C...another object of the present invention is to provide a reconstituted cascade reaction system which is not susceptible to reaction inhibition even in the presence of a salt (ion)" (paragraphs 14 and 15).

The breadth of the claims: Claim 43 (claims 56 and 57 dependent therefrom) is drawn to a genus of horseshoe crab Factor C polypeptides having activity of Factor C. According to the specification, "the activity of Factor C refers to such an activity that the Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B" (spec at p. 36, paragraph 28).

Claim 44 is drawn to the Factor C according to claim 43, which is a recombinant protein. According to the specification, the term "recombinant protein" refers to a protein obtained through introduction of a gene encoding the protein into a host cell and heterologous expression of the gene (paragraph 19).

Claim 45 is drawn to the Factor C according to claim 43, which contains (α -2,3) linked terminal sialic acid.

Claim 46 is drawn to the Factor C according to claim 45, which contains (α -2,3) linked terminal sialic acid in a greater amount, as compared with a native Factor C and/or a horseshoe crab Factor C expressed in Sf9 as a host cell.

Claim 47 is drawn to the Factor C according to claim 43, which exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate.

Claim 48 is drawn to the Factor C according to claim 43, which has a molecular weight of 115 kDa to 140 kDa or a molecular weight of 127 kDa $\pm$ 5 kDa, as measured through SDS-PAGE under a non-reducing condition.

Claim 49 is drawn to (in relevant part) the Factor C according to claim 43, which is a protein shown in the following (A), (B), (C), or (D):

(A) a protein comprising the amino acid sequence shown in SEQ ID NO: 2; and

(B) a protein comprising the amino acid sequence shown in SEQ ID NO:2 but which includes substitution, deletion, insertion, or addition of one or several amino acid residues, and having activity of Factor C.

As noted above, according to the specification, "the activity of Factor C refers to such an activity that the Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B" (spec at p. 36, paragraph 28). The structure of the Factor C is unlimited.

Claim 50 is drawn to the Factor C according to claim 43, which is water-soluble.

Claim 54 (claims 62 and 63 dependent therefrom) is drawn to a horseshoe crab Factor C producible by a method comprising expressing the horseshoe crab Factor C in a mammalian cell as a host cell.

The claims encompass non-functional horseshoe crab Factor C polypeptides.

Claim 55 is drawn to the Factor C according to claim 43, which is producible by a method comprising expressing the horseshoe crab Factor C in a mammalian cell as a host cell.

(C) The state of the prior art; (D) The level of one of ordinary skill; and (E) The level of predictability in the art: While one of skill in the art would have expected a horseshoe crab Factor C polypeptide that is isolated from its natural source to have activity of Factor C, the specification supports a high level of unpredictability regarding

the activity of a horseshoe crab Factor C that is recombinantly expressed in a heterologous host cell. For example, the specification discloses that a horseshoe crab Factor C that is recombinantly expressed in a *Drosophila* S2 cell does not have Factor C activity (paragraph 132). Also, regarding the terminal sialic acid, residual activity in the presence of sodium citrate, molecular weight, amino acid sequence, solubility, and expression in a mammalian cell, the specification supports a high level of unpredictability regarding the terminal sialic acid, residual activity in the presence of sodium citrate, molecular weight, amino acid sequence, solubility, and expression in a mammalian cell of a horseshoe crab Factor C that is recombinantly expressed. For example, regarding the terminal sialic acid, the specification discloses that a horseshoe crab Factor C that is recombinantly expressed in Sf9 cells does not have any (α -2,3) linked terminal sialic acid, while Factor C that is recombinantly expressed in CHO and HEK cells contains (α -2,3) linked terminal sialic acid (paragraph 154). Regarding residual activity in the presence of sodium citrate, Figure 7 shows that Factor C that is recombinantly expressed in Sf9 cells has almost no residual activity in the presence of 21 mM sodium citrate, Factor C that is recombinantly expressed in CHO and HEK cells retains about 25% residual activity in the presence of 21 mM sodium citrate. Regarding molecular weight, the specification discloses that a horseshoe crab Factor C that is recombinantly expressed in Sf9 cells has a molecular weight of 109 kDa, while the same Factor C that is recombinantly expressed in CHO and HEK cells has a molecular weight of 128 or 124 kDa, respectively (Table 1). Regarding amino acid sequence, the specification fails to identify any alterations to the amino acid sequence of SEQ ID NO:

2 that can be made and still have the identity of a horseshoe crab Factor C polypeptide and as described above, the same horseshoe crab Factor C expressed in different host cells can have very different characteristics and even be non-functional. Regarding solubility, the specification discloses that a horseshoe crab Factor C that is recombinantly expressed in COS cells is insoluble (paragraph 11).

(F) The amount of direction provided by the inventor and (G) The existence of working examples: The specification discloses the following working examples of a horseshoe crab Factor C as encompassed by the claims, *i.e.*, Factor C isolated from *Tachypleus tridentatus* or *Carcinoscorpius rotundicauda* hemocyte lysate and *Tachypleus tridentatus* Factor C expressed in Sf9 insect cells, CHO cells, or HEK cells. Other than these working examples, the specification fails to disclose any other working examples of a horseshoe crab Factor C as encompassed by the claims and other than *Tachypleus tridentatus* Factor C expressed in Sf9 insect cells, CHO cells, or HEK cells, the specification fails to provide guidance regarding the combination of horseshoe crab Factor C and expression hosts, particularly mammalian expression hosts, that are useful in accordance with the invention. The specification further fails to disclose how to use non-functional horseshoe crab Factor C polypeptides as encompassed by claim 54.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the state of the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner

reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this

Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim(s) 43, 44, 49, 50, 56, and 57 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Mizumura et al. (WO 2012/118226 A1; cited on the IDS filed on 6/9/2015; hereafter “Mizumura”).

Claims 43, 44, 49, and 50 are drawn to a horseshoe crab Factor C having activity of Factor C. According to the specification, “the activity of Factor C refers to such an activity that the Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B” (spec at p. 36, paragraph 28).

Claim 56 is drawn to an endotoxin assay agent containing the Factor C according to claim 43.

Claim 57 is drawn to an endotoxin assay kit comprising the assay agent according to claim 56.

Regarding claims 43 and 44, Mizumura teaches recombinant production of a *Tachypleus tridentatus* factor C polypeptide using insect Sf9 cells as an expression host cell (Example 1, beginning at paragraph 81), which has activity to convert Factor B into activated Factor B as measured by proclotting enzyme-activating capacity (Example 2-2, beginning at paragraph 101).

Regarding claim 49, Mizumura teaches the amino acid sequence of *Tachypleus tridentatus* factor C is SEQ ID NO: 2, which has 100% sequence identity to the amino acid sequence of SEQ ID NO: 2 herein (see Appendix A sequence alignment).

Regarding claim 50, Mizumura teaches the factor C is present in the culture broth (Example 1-2-2, paragraph 97) and thus the factor C is considered to be water-soluble.

Regarding claim 56, Mizumura teaches an endotoxin measuring agent comprising the *Tachypleus tridentatus* factor C polypeptide (paragraph 17).

Regarding claim 57, Mizumura teaches the endotoxin measuring agent may be provided as an endotoxin-measuring kit (paragraph 47).

This anticipates claims 43, 44, 49, 50, 56, and 57 as written.

10. Claim(s) 54, 62, and 63 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Koshiba et al. (*J. Biol. Chem.* 282:3962-3967, 2007; cited on the attached Form PTO-892; hereafter "Koshiba").

Claim 54 is drawn to a horseshoe crab Factor C producible by a method comprising expressing the horseshoe crab Factor C in a mammalian cell as a host cell.

Claim 62 is drawn to an endotoxin assay agent containing the Factor C according to claim 54.

Claim 63 is drawn to an endotoxin assay kit comprising the assay agent according to claim 62.

Regarding claim 54, Koshiba teaches recombinant production of a *Tachypleus tridentatus* factor C polypeptide light chain and heavy chain using HEK293 cells (p. 3963, paragraph bridging columns 1 and 2).

Regarding claims 62 and 63, Koshiba teaches forming a complex of the factor C polypeptide heavy chain and LPS (p. 3964, Figure 2; p. 3966, paragraph bridging columns 1 and 2), which is considered to be an endotoxin assay agent and an endotoxin assay kit as encompassed by claims 62 and 63, respectively.

This anticipates claims 54, 62, and 63 as written.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claim(s) 43-46, 48-50, 56, and 57 are rejected under pre-AIA 35 U.S.C. 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. 103(a) as obvious over Nakamura et al. (*J. Biochem.* 99:847-857, 1986; cited on the IDS filed on 6/9/2015; hereafter “Nakamura”) as evidenced by Mizumura (*supra*). See MPEP 2112.III regarding a rejection under 35 U.S.C. 102/103. See MPEP 2131.01 regarding a multiple reference 35 U.S.C. 102 rejection.

Claims 43-46 and 48-50 are drawn to a horseshoe crab Factor C having activity of Factor C. According to the specification, “the activity of Factor C refers to such an activity that the Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B” (spec at p. 36, paragraph 28).

Claim 56 is drawn to an endotoxin assay agent containing the Factor C according to claim 43.

Claim 57 is drawn to an endotoxin assay kit comprising the assay agent according to claim 56.

Regarding claim 43, Nakamura teaches an activated factor C polypeptide purified from the hemocyte lysate of *Tachypleus tridentatus* (p. 848, sentence bridging columns 1 and 2). Nakamura teaches activation of factor B by the activated factor C (p. 851, column 2).

Regarding claim 44, according to the specification, the term "recombinant protein" refers to a protein obtained through introduction of a gene encoding the protein into a host cell and heterologous expression of the gene (paragraph 19). The recitation of "recombinant" is interpreted as a "product-by-process" limitation and because the claim does not limit the "host cell" from which the protein is heterologously expressed, the recitation of "recombinant" fails to structurally and/or functionally distinguish the claimed horseshoe crab factor C from Nakamura's factor C polypeptide.

Regarding claim 45, Nakamura does not teach the activated factor C polypeptide purified from the hemocyte lysate of *T. tridentatus* has (α -2,3) linked terminal sialic acid. However, the specification teaches that factor C polypeptide derived from *T. tridentatus* reacts with a (α -2,3)-linked terminal sialic acid-specific lectin (paragraph 153). As such, since Nakamura's activated factor C polypeptide is derived from *T. tridentatus*, it follows that Nakamura's activated factor C polypeptide necessarily has (α -2,3)-linked terminal sialic acid.

Regarding claim 46, Nakamura does not teach the activated factor C polypeptide purified from the hemocyte lysate of *T. tridentatus* has (α -2,3) linked terminal sialic acid in a greater amount as compared with a horseshoe crab Factor C expressed in Sf9 as a host cell. However, as noted above, the specification teaches that factor C polypeptide

derived from *T. tridentatus* has (α -2,3)-linked terminal sialic acid (paragraph 153), while *T. tridentatus* factor C polypeptide expressed in Sf9 as a host cell does not have any (α -2,3) linked terminal sialic acid (paragraph 154). As such, since factor C polypeptide derived from *T. tridentatus* has (α -2,3)-linked terminal sialic acid and since *T. tridentatus* factor C polypeptide expressed in Sf9 as a host cell does not have any (α -2,3) linked terminal sialic acid, it follows that Nakamura's activated factor C polypeptide purified from *T. tridentatus* necessarily has a greater amount of (α -2,3)-linked terminal sialic acid than *T. tridentatus* factor C polypeptide expressed in Sf9 as a host cell.

Regarding claim 48, Nakamura does not teach the activated factor C polypeptide purified from the hemocyte lysate of *T. tridentatus* has a molecular weight as recited in the claim. However, the specification teaches that factor C polypeptide derived from *T. tridentatus* has a molecular weight of 124 kDa by SDS-PAGE under non-reducing conditions (paragraph 144 and Table 1). As such, since Nakamura's activated factor C polypeptide is derived from *T. tridentatus*, it follows that Nakamura's activated factor C polypeptide necessarily has a molecular weight of 124 kDa by SDS-PAGE under non-reducing conditions.

Regarding claim 49, Nakamura does not teach the amino acid sequence of the activated factor C polypeptide purified from the hemocyte lysate of *T. tridentatus* has the amino acid sequence of SEQ ID NO: 2. However, evidentiary reference of Mizumura is cited to show that the amino acid sequence of *Tachypleus tridentatus* factor C is identical to SEQ ID NO: 2 herein (see Appendix A sequence alignment).

Regarding claim 50, Nakamura teaches the factor C has catalytic activity in an aqueous buffer (p. 852, Figure 6) and thus the factor C is considered to be water-soluble.

Regarding claims 56 and 57, Nakamura teaches reconstitution of the LPS-mediated clotting system, including the activated factor C polypeptide purified from the hemocyte lysate of *T. tridentatus*, which is considered to be an endotoxin assay agent and an endotoxin assay kit as encompassed by claims 56 and 57, respectively.

This anticipates claims 43-46, 48-50, 56, and 57 as written.

12. Claim(s) 43-50, 54-57, 62, and 63 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Ding et al. (US 5,716,834; cited on the attached Form PTO-892; hereafter "Ding") as evidenced by Mizumura (*supra*). See MPEP 2112.III regarding a rejection under 35 U.S.C. 102/103. See MPEP 2131.01 regarding a multiple reference 35 U.S.C. 102 rejection.

Claims 43-50 and 55 are drawn to a horseshoe crab Factor C having activity of Factor C. According to the specification, "the activity of Factor C refers to such an activity that the Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B" (spec at p. 36, paragraph 28).

Claim 54 is drawn to a horseshoe crab Factor C producible by a method comprising expressing the horseshoe crab Factor C in a mammalian cell as a host cell.

Claims 56 and 62 are drawn to an endotoxin assay agent containing the Factor C according to claim 43 and 54, respectively.

Claims 57 and 63 are drawn to an endotoxin assay kit comprising the assay agent according to claims 56 and 62, respectively.

Regarding claims 43, 44, 54, and 55, the reference of Ding teaches a mammalian host cell transformed with a recombinant vector for expressing a Factor C (column 2, lines 46-55). Ding teaches a method for producing the Factor C by culturing the host cell and recovering the Factor C protein (column 2, lines 58-63). Ding teaches mammalian host cells include Chinese Hamster Ovary cells (column 19, lines 39-43). Ding teaches there are four species of horseshoe crab, including *T. tridentatus* (column 1, lines 18-20). Ding teaches activation of the Factor C by endotoxin (column 2, lines 7-9).

Regarding claim 45, Ding does not teach the activated factor C polypeptide recombinantly expressed and recovered from CHO cells has (α -2,3) linked terminal sialic acid. However, the specification teaches that factor C polypeptide recombinantly expressed and recovered from CHO cells has (α -2,3)-linked terminal sialic acid (paragraph 154). As such, since Ding teaches the embodiment of recombinantly expressing and recovering *T. tridentatus* factor C from CHO cells and activating the factor C by endotoxin, it follows that Ding's activated factor C polypeptide necessarily has (α -2,3)-linked terminal sialic acid.

Regarding claim 46, Ding does not teach the activated *T. tridentatus* factor C polypeptide recombinantly expressed and recovered from CHO cells has (α -2,3) linked terminal sialic acid in a greater amount as compared with a horseshoe crab Factor C expressed in Sf9 as a host cell. However, the specification teaches that factor C

polypeptide recombinantly expressed and recovered from CHO cells has (α -2,3) linked terminal sialic acid (paragraph 154), while *T. tridentatus* factor C polypeptide expressed in Sf9 as a host cell does not have any (α -2,3) linked terminal sialic acid (paragraph 154). As such, since *T. tridentatus* factor C recombinantly expressed and recovered from CHO cells has (α -2,3)-linked terminal sialic acid and since *T. tridentatus* factor C polypeptide expressed in Sf9 as a host cell does not have any (α -2,3) linked terminal sialic acid, it follows that Ding's activated factor C polypeptide recombinantly expressed and recovered from CHO cells necessarily has a greater amount of (α -2,3)-linked terminal sialic acid than *T. tridentatus* factor C polypeptide expressed in Sf9 as a host cell.

Regarding claim 47, Ding does not teach the activated *T. tridentatus* factor C polypeptide recombinantly expressed and recovered from CHO cells exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate. However, the Figure 7 of this application shows that *T. tridentatus* factor C polypeptide recombinantly expressed and recovered from CHO cells exhibits a residual activity of 10% or higher in the presence of 10% sodium citrate with a dilution factor of 8, which, according to the specification is about 21 mM sodium citrate (p. 87). As such, since *T. tridentatus* factor C recombinantly expressed and recovered from CHO cells recombinantly expressed and recovered from CHO cells exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate, it follows that Ding's activated factor C polypeptide recombinantly expressed and recovered from CHO cells necessarily exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate.

Regarding claim 48, Ding does not teach the activated *T. tridentatus* factor C polypeptide recombinantly expressed and recovered from CHO cells has a molecular weight as recited in the claim. However, the specification teaches that *T. tridentatus* factor C polypeptide recombinantly expressed and recovered from CHO cells has a molecular weight of 128 kDa by SDS-PAGE under non-reducing conditions (paragraph 144 and Table 1). As such, since Ding's activated *T. tridentatus* factor C polypeptide is recombinantly expressed and recovered from CHO cells, it follows that Ding's activated factor C polypeptide necessarily has a molecular weight of 128 kDa by SDS-PAGE under non-reducing conditions.

Regarding claim 49, Ding does not teach the amino acid sequence of *T. tridentatus* factor C has the amino acid sequence of SEQ ID NO: 2. However, evidentiary reference of Mizumura is cited to show that the amino acid sequence of *T. tridentatus* factor C is identical to SEQ ID NO: 2 herein (see Appendix A sequence alignment).

Regarding claim 50, Ding teaches the factor C can be secreted into the culture medium (column 3, lines 47-48) and thus the factor C is considered to be water-soluble.

Regarding claims 56, 57, 62, and 63, Ding teaches the recombinant Factor C may be employed in a chromogenic assay, wherein upon activation by endotoxin, the Factor C converts the substrate to a colored product, thereby detecting and quantifying endotoxin (column 2, lines 7-11), which is considered to be an endotoxin assay agent and an endotoxin assay kit as encompassed by claims 56, 57, 62, and 63 respectively.

This anticipates claims 43-46, 48-50, 56, and 57 as written.

13. Claim(s) 43-50, 54-57, 62, and 63 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Ding et al. (US 5,858,706; cited on the IDS filed on 6/9/2015; hereafter "Ding2") as evidenced by Mizumura (*supra*). See MPEP 2112.III regarding a rejection under 35 U.S.C. 102/103. See MPEP 2131.01 regarding a multiple reference 35 U.S.C. 102 rejection.

Claims 43-50 and 55 are drawn to a horseshoe crab Factor C having activity of Factor C. According to the specification, "the activity of Factor C refers to such an activity that the Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B" (spec at p. 36, paragraph 28).

Claim 54 is drawn to a horseshoe crab Factor C producible by a method comprising expressing the horseshoe crab Factor C in a mammalian cell as a host cell.

Claims 56 and 62 are drawn to an endotoxin assay agent containing the Factor C according to claim 43 and 54, respectively.

Claims 57 and 63 are drawn to an endotoxin assay kit comprising the assay agent according to claims 56 and 62, respectively.

Regarding claims 43, 44, 54, and 55, the reference of Ding2 teaches a mammalian host cell transformed with a recombinant vector for expressing a cDNA encoding a Factor C (column 9, Example 1). Ding2 teaches a method for producing the Factor C by culturing the host cell and recovering the Factor C protein (column 9, Example 1). Ding2 teaches mammalian host cells include Chinese Hamster Ovary cells (column 9, Example 1). Ding2 teaches the cDNA for expression encodes a T.

tridentatus horseshoe crab Factor C (column 3, lines 14-20). Ding2 teaches activation of the Factor C by endotoxin (column 1, lines 44-47).

Regarding claim 45, Ding2 does not teach the activated factor C polypeptide recombinantly expressed and recovered from CHO cells has (α -2,3) linked terminal sialic acid. However, the specification teaches that factor C polypeptide recombinantly expressed and recovered from CHO cells has (α -2,3)-linked terminal sialic acid (paragraph 154). As such, since Ding2 teaches the embodiment of recombinantly expressing and recovering *T. tridentatus* factor C from CHO cells and activating the factor C by endotoxin, it follows that Ding2's activated factor C polypeptide necessarily has (α -2,3)-linked terminal sialic acid.

Regarding claim 46, Ding2 does not teach the activated *T. tridentatus* factor C polypeptide recombinantly expressed and recovered from CHO cells has (α -2,3) linked terminal sialic acid in a greater amount as compared with a horseshoe crab Factor C expressed in Sf9 as a host cell. However, the specification teaches that factor C polypeptide recombinantly expressed and recovered from CHO cells has (α -2,3) linked terminal sialic acid (paragraph 154), while *T. tridentatus* factor C polypeptide expressed in Sf9 as a host cell does not have any (α -2,3) linked terminal sialic acid (paragraph 154). As such, since *T. tridentatus* factor C recombinantly expressed and recovered from CHO cells has (α -2,3)-linked terminal sialic acid and since *T. tridentatus* factor C polypeptide expressed in Sf9 as a host cell does not have any (α -2,3) linked terminal sialic acid, it follows that Ding2's activated factor C polypeptide recombinantly expressed and recovered from CHO cells necessarily has a greater amount of (α -2,3)-

linked terminal sialic acid than *T. tridentatus* factor C polypeptide expressed in Sf9 as a host cell.

Regarding claim 47, Ding2 does not teach the activated *T. tridentatus* factor C polypeptide recombinantly expressed and recovered from CHO cells exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate. However, the Figure 7 of this application shows that *T. tridentatus* factor C polypeptide recombinantly expressed and recovered from CHO cells exhibits a residual activity of 10% or higher in the presence of 10% sodium citrate with a dilution factor of 8, which, according to the specification is about 21 mM sodium citrate (p. 87). As such, since *T. tridentatus* factor C recombinantly expressed and recovered from CHO cells recombinantly expressed and recovered from CHO cells exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate, it follows that Ding2's activated factor C polypeptide recombinantly expressed and recovered from CHO cells necessarily exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate.

Regarding claim 48, Ding2 does not teach the activated *T. tridentatus* factor C polypeptide recombinantly expressed and recovered from CHO cells has a molecular weight as recited in the claim. However, the specification teaches that *T. tridentatus* factor C polypeptide recombinantly expressed and recovered from CHO cells has a molecular weight of 128 kDa by SDS-PAGE under non-reducing conditions (paragraph 144 and Table 1). As such, since Ding's activated *T. tridentatus* factor C polypeptide is recombinantly expressed and recovered from CHO cells, it follows that Ding2's

activated factor C polypeptide necessarily has a molecular weight of 128 kDa by SDS-PAGE under non-reducing conditions.

Regarding claim 49, Ding2 does not teach the amino acid sequence of *T. tridentatus* factor C has the amino acid sequence of SEQ ID NO: 2. However, evidentiary reference of Mizumura is cited to show that the amino acid sequence of *T. tridentatus* factor C is identical to SEQ ID NO: 2 herein (see Appendix A sequence alignment).

Regarding claim 50, Ding2 teaches solubilization of the factor C (column 7, lines 456-53) and thus the factor C is considered to be water-soluble.

Regarding claims 56, 57, 62, and 63, Ding2 teaches the recombinant Factor C for use in an assay for endotoxin detection and teaches elements for conducting such an assay (column 8, lines 50-60), which is considered to be an endotoxin assay agent and an endotoxin assay kit as encompassed by claims 56, 57, 62, and 63 respectively.

This anticipates claims 43-46, 48-50, 56, and 57 as written.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

14. Claims 43-46, 48-50, 56, and 57 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more.

Claims 43-46 and 48-50 are drawn to a horseshoe crab Factor C having activity of Factor C. According to the specification, “the activity of Factor C refers to such an activity that the Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B (spec at p. 36, paragraph 28).

Claim 56 is drawn to an endotoxin assay agent containing the Factor C according to claim 43.

Claim 57 is drawn to an endotoxin assay kit comprising the assay agent according to claim 56.

Given a broadest reasonable interpretation, the horseshoe crab Factor C of claims 43-46 and 48-50 encompasses a naturally occurring horseshoe crab Factor C, *e.g.*, activated factor C polypeptide present in the hemocytes of *T. tridentatus*. Also, the endotoxin assay agent and endotoxin assay kit of claims 56 and 57, which do not recite any additional element(s) of the endotoxin assay agent and endotoxin assay kit other than the horseshoe crab Factor C itself, encompass naturally occurring horseshoe crab hemocytes comprising an activated Factor C. Thus, the claims are considered to encompass naturally occurring products. Because there is no difference in characteristics (structural, functional, or otherwise) between the claimed and naturally occurring products, the claimed products do not have markedly different characteristics from what exists in nature, and thus are a “product of nature” exception. Accordingly, the claims are directed to a judicial exception. Because the claims do not include any additional features that could add significantly more to the exception, the claims do not qualify as eligible subject matter.

Conclusion

Status of the claims:

Claims 43-64 are pending.

Claims 51-53, 58-61, and 64 are withdrawn from consideration.

Claims 43-50, 54-57, 62, and 63 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656

Art Unit: 1656

APPENDIX A

AZZ33066

ID AZZ33066 standard; protein; 1019 AA.

XX

AC AZZ33066;

XX

DT 25-OCT-2012 (first entry)

XX

DE Tachypleus tridentatus factor C, SEQ ID 2.

XX

KW factor C; protein production; protein quantitation; BOND_PC;

KW limulus factor C precursor; limulus factor C; G04252; G05215; G05515;

KW G05529; G06508; G06810; G07155; G08233; G016020; G016021; G016787;

KW G042381.

XX

OS Tachypleus tridentatus.

XX

CC PN WO2012118226-A1.

XX

CC PD 07-SEP-2012.

XX

CC PF 28-FEB-2012; 2012WO-JP055728.

XX

PR 28-FEB-2011; 2011US-0447556P.

XX

CC PA (SEKG) SEIKAGAKU CORP.

XX

CC PI Mizumura H, Aizawa M, Oda T;

XX

DR WPI; 2012-L75079/61.

DR N-PSDB; AZZ33065, AZZ33071.

DR PC:NCBI; gi585398.

DR PC:SWISSPROT; P28175.

XX

CC PT Agent useful for measuring endotoxin, comprises factor C derived from

CC PT Tachypleus tridentatus, factor B of horseshoe crab and proclotting enzyme

CC PT of horseshoe crab.

XX

CC PS Claim 3; SEQ ID NO 2; 72pp; English.

XX

CC The present invention relates to a novel agent, useful for measuring
 CC endotoxin. The agent comprises: (a) a factor C derived from Tachypleus
 CC tridentatus, wherein factor C does not have his-tag sequence at the C-
 CC terminal region; (b) a factor B derived from horseshoe crab; and (c) a
 CC proclotting enzyme derived from horseshoe crab. The invention also
 CC provides: a method for producing the endotoxin measuring agent by (a)
 CC incorporating a DNA sequence encoding the factor C, factor B and
 CC proclotting enzyme, into a viral DNA, (b) infecting insect cells with the
 CC virus incorporated with the DNA, (c) allowing the infected insect cells
 CC to express the protein; and a method for measuring endotoxin in a test
 CC sample. The present sequence represents a specifically claimed Tachypleus
 CC tridentatus factor C, which can be produced by the above mentioned
 CC endotoxin measuring agent production method, for measuring endotoxin.

CC

CC Revised record issued on 18-OCT-2012 : Enhanced with precomputed
 CC information from BOND.

XX

SQ Sequence 1019 AA;

Query Match 100.0%; Score 5619; DB 19; Length 1019;

Best Local Similarity 100.0%;

Matches 1019; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 MVLASFLVSGVLVLGILAQQMRPVQSRGVDLGLCDETRFECKCGDPGYVFNVPKQCTYFY 60
 |||

Art Unit: 1656

	1	MVLASFLVSGLVGLGILAQQMRPVQSRGVDLGLCDETRFECKCGDPPGYVFNVPMKQCTYFY	60
Qy	61	RWRPYCKPCDDLEAKDICPKYKRCQECKAGLDSCVTCPPNKYGTWCSGECQCKNGGICDQ	120
Db	61	RWRPYCKPCDDLEAKDICPKYKRCQECKAGLDSCVTCPPNKYGTWCSGECQCKNGGICDQ	120
Qy	121	RTGACTCRDRYEGAHCEILKGCPLLPDSQVQEVNRNPPDPNPQTIDYSCSPGFKLKGVARI	180
Db	121	RTGACTCRDRYEGAHCEILKGCPLLPDSQVQEVNRNPPDPNPQTIDYSCSPGFKLKGVARI	180
Qy	181	SCLPNGQWSSFPKPCIRECAKVSSPEHGKVNAPSGNMIEGATLRFSCDSPYYLIGQETLT	240
Db	181	SCLPNGQWSSFPKPCIRECAKVSSPEHGKVNAPSGNMIEGATLRFSCDSPYYLIGQETLT	240
Qy	241	CQNGNGWSSGQIPQCKKLVFCDPLDPVNHAEHQVKIGVEQKYGQFPQGTETVYTCSGNYFL	300
Db	241	CQNGNGWSSGQIPQCKKLVFCDPLDPVNHAEHQVKIGVEQKYGQFPQGTETVYTCSGNYFL	300
Qy	301	MGFNTLKCNPDGWSWGSQSPSCVKVADREVDGCDKAVDFLDDVGEPVRIHCPAGCSLTAGT	360
Db	301	MGFNTLKCNPDGWSWGSQSPSCVKVADREVDGCDKAVDFLDDVGEPVRIHCPAGCSLTAGT	360
Qy	361	VWGTAIYHELSSVCRAAIHAGKLPNSGGAVHVNNPGPYSDFLGSDLNGIKSEELKSLARS	420
Db	361	VWGTAIYHELSSVCRAAIHAGKLPNSGGAVHVNNPGPYSDFLGSDLNGIKSEELKSLARS	420
Qy	421	FRFDYVSSSTAGRSGCPDGWFVEVEENCYVYTSKQRAWERAQGVCCTNMAARLAVLDKDLIP	480
Db	421	FRFDYVSSSTAGRSGCPDGWFVEVEENCYVYTSKQRAWERAQGVCCTNMAARLAVLDKDLIP	480
Qy	481	SSLTETLRGKGLTTTWIGLHRLDAEKPFVWELMDRSNVVNDNLTFWASGEPGNETNCVY	540
Db	481	SSLTETLRGKGLTTTWIGLHRLDAEKPFVWELMDRSNVVNDNLTFWASGEPGNETNCVY	540
Qy	541	LDIRDQLQPWVKTKSCFQPSFACMMDLSDRNKAKCDDPGPLENHATLHGQSIDGFYAG	600
Db	541	LDIRDQLQPWVKTKSCFQPSFACMMDLSDRNKAKCDDPGPLENHATLHGQSIDGFYAG	600
Qy	601	SSIRYSCEVLHYLSGTETVTCTTNGTWSAPKPRCIKIVITCQNPPVPSYGSVEIKPPSRTN	660
Db	601	SSIRYSCEVLHYLSGTETVTCTTNGTWSAPKPRCIKIVITCQNPPVPSYGSVEIKPPSRTN	660
Qy	661	SISRVGSPFLRLPRLPLPLARAAPPPKPRSSQPSVVDLASKVKLPEGHYRVGSRAIYTC	720
Db	661	SISRVGSPFLRLPRLPLPLARAAPPPKPRSSQPSVVDLASKVKLPEGHYRVGSRAIYTC	720
Qy	721	ESRYEYLLGSQGRRCDSNGNWSGRPASCPVCGRSDSPRSPFIWNGNSTEIGQWPWQAGI	780
Db	721	ESRYEYLLGSQGRRCDSNGNWSGRPASCPVCGRSDSPRSPFIWNGNSTEIGQWPWQAGI	780
Qy	781	SRWLADHNMWFLQCGGSLLEKWIIVTAAHCVTYSATAEIIDPSQFKIYLGKYYRDSRDD	840
Db	781	SRWLADHNMWFLQCGGSLLEKWIIVTAAHCVTYSATAEIIDPSQFKIYLGKYYRDSRDD	840
Qy	841	DYVQVREALEIHVNPNDPGNLNFDIALIQLKTPVTLTTRVQPICLPTDITTREHLKEGT	900
Db	841	DYVQVREALEIHVNPNDPGNLNFDIALIQLKTPVTLTTRVQPICLPTDITTREHLKEGT	900
Qy	901	LAVVTGWGLNENNTYSEMIQAVLPVVAASTCEEYKEADLPLTVTENMFCAGYKKGRYD	960
Db	901	LAVVTGWGLNENNTYSEMIQAVLPVVAASTCEEYKEADLPLTVTENMFCAGYKKGRYD	960
Qy	961	ACSGDSGGPLVFADDSRTERRVWLEGIVSWGSPSGCGKANQYGGFTKVNVLFSWIRQFI	1019
Db	961	ACSGDSGGPLVFADDSRTERRVWLEGIVSWGSPSGCGKANQYGGFTKVNVLFSWIRQFI	1019