

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHARLES RIVER LABORATORIES, INC.,

Petitioner,

v.

SEIKAGAKU CORPORATION,

Patent Owner.

Case No. IPR2025-00440

Patent No. 11,236,318

PATENT OWNER SUR-REPLY

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TABLE OF EXHIBITS

<u>Exhibit No.</u>	<u>Description</u>
2001	Excerpt from U.S. Application No. 14/650,767 File History – Claims dated June 9, 2015
2002	Excerpt from U.S. Application No. 14/650,767 File History – Non-Final Rejection dated September 16, 2016
2003	FAQs for Interim Processes for PTAB Workload Management, available at https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management
2004	Declaration of Michael A. Frohman, M.D., Ph.D. and exhibits from Opposition for European Patent No. 3530670
2005	Notice of Opposition to European Patent No. 3441466
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2007	Extract from the Register of European Patents for European Patent No. 4291648
2008	Ding, et al., “Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ,” Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in Opposition to European Patent No. 3441466
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2100	Predicted 3-D structure comparisons for <i>Limulus polyphemus</i> and <i>Tachypleus tridentatus</i> Factor C
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2108 [NEW]	Second Declaration of Brian Schaefer, Ph.D.

I. INTRODUCTION

Petitioner's Reply (Paper 32) ("Reply") imposes a heightened burden on Patent Owner ("PO") beyond what is required in the law to demonstrate Section 112 support for the challenged claim. Ignoring that sequence information for *Limulus polyphemus* Factor C existed in the art before the December 10, 2013 priority date, Petitioner instead maintains its position that the claim lacks written description support because the specification does not include this sequence information within its four corners. But the law does not require such disclosure.

Further undermining Petitioner's position, it repeatedly proffers inconsistent arguments that undermine Petitioner's credibility. *First*, while in this proceeding Petitioner argues it would not have been routine to characterize the sequence of *Limulus polyphemus* Factor C, it argued the opposite before the European Patent Office ("EPO") in challenging one of PO's European patents. *Second*, while Petitioner argues predictions cannot be made as to residual activity in the claimed *Limulus polyphemus* Factor C based on residual activity in *Tachypleus tridentatus* to support its Section 112 attack, it argues the opposite in its obviousness attack.

As such, the patentability of claim 21 of the '318 Patent should be upheld.

II. CLAIM 21 IS ENTITLED TO ITS DECEMBER 10, 2013 EFFECTIVE FILING DATE

A. The '767 Application Provides Written Description Support

1. The Coding Sequences for *Limulus polyphemus* Factor C were Known in 2013

Petitioner continues to misapply the law by pointing to the lack of *Limulus polyphemus* Factor C sequence data in the '767 Application to support its written description attack. Reply at 8-9. But Petitioner's argument ignores that claim 21 relates to *Limulus polyphemus* Factor C protein that had been isolated and studied long before the 2013 priority date, Paper 26 at 3-5, and that the law does not require disclosure of sequence data already known in the art. *See, e.g., Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367-1368 (Fed. Cir. 2006) ("When the prior art includes the nucleotide information" or accessible sources provide the necessary sequence information "satisfaction of the written description requirement does not require either the recitation or incorporation by reference... of such genes and sequences."); *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005) ("When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh.").

As explained in PO's Response, by **October 31, 2013**, the following information was publicly available: (i) a 188 Mb *Limulus polyphemus* cDNA amoebocyte transcriptome under BioProject accession number PRJNA178588; and

(ii) a 4 Gb shotgun sequence of the *Limulus polyphemus* genome under BioProject accession number PRJNA178587.¹ Paper 26 at 16-17. And by **December 2013**, a POSA could have used this data to assemble 97.2% of the full Factor C coding sequence and then used standard methods to recover the remaining sequence. *Id.*

Petitioner does not contest the existence of this sequence information, nor can it.² Instead, Petitioner argues that “PO goes **well beyond** background knowledge” and “improperly augments the ’767 Application.” Reply at 8 (emphasis in original). Not only does Petitioner fail to support these conclusions, but its argument

¹ Petitioner incorrectly refers to this data as “bulk sequence data of the whole transcriptome for the *Limulus polyphemus* horseshoe crab.” Reply at 9. The deposit Dr. Schaefer analyzed was the transcriptome from *Limulus polyphemus* amoebocytes. Ex. 2038 ¶¶ 36, 61. This data set contains cDNA sequences only, isolated from the very cell type in which Factor C is present. The narrowness of the data set significantly reduces the sequence analysis needed to reassemble the protein sequence as compared to starting from whole genome data. *Id.* ¶ 72.

² Although Petitioner notes PO’s expert did not verify the publication date, Reply at 9, Petitioner has waived any objection to this publication date. 37 C.F.R. § 42.64.

contradicts arguments it made before the EPO in Opposition proceedings regarding the routine nature of characterizing the *Limulus polyphemus* Factor C sequence.³

Specifically, in the Opposition, Petitioner conceded that the '767 Application “discloses methods for recombinantly producing Factor C . . . and directly points the skilled person to carry out this method with a *Factor C derived from Limulus polyphemus species*.” Ex. 1048 ¶ 30.⁴ Petitioner also conceded *Limulus* Factor C protein “was a *well-known, publicly available protein*, the specific amino acid sequence . . . ‘*being an inherent property of the protein*,’ such that it would have been a matter of “**routine analysis**” to characterize the sequence of *Limulus polyphemus* Factor C. *Id.* ¶ 31; *see also id.* ¶¶ 32-37, 56 (noting “it was *common general knowledge* that *the Limulus* Factor C had been used for decades”); *id.* ¶ 59 (admitting “it is a matter of routine practice for a person skilled in the art to determine the sequence of a known protein”); Paper 26 at 38-41.

³ After PO filed two motions to compel additional discovery (Paper Nos. 12, 23), Petitioner finally confirmed that it “is ‘the party behind the European Opposition proceeding.’” Paper 31 at 2.

⁴ D1 is EP 2939241, which is a European patent filed December 10, 2013 and having the same specification as the '767 Application. Ex. 1048 ¶¶ 4, 51.

Petitioner also conceded that “the use of Factor C derived from *Limulus polyphemus* is explicitly disclosed as one of the specific ‘*Modes for Carrying Out the Invention*’” of the ’767 Application and noted that PO told the PTO “that the skilled person reading the description of [the ’767 Application] would ***not only be able to produce a Limulus Factor C without undue burden***, but that they would further expect the invention of [the ’767 Application] to ‘*also work when Factor C is the Factor C of Limulus polyphemus.*’” Ex. 1048 ¶¶ 48, 50.

Any attempt here by Petitioner to assert the opposite should thus be viewed with skepticism and undermining Petitioner’s credibility.⁵ See *Provepharm Inc. v. Wista Lab’ys Ltd.*, No. IPR2018-00323, 2019 WL 2865314, at *15 (P.T.A.B. July 2, 2019) (noting that Petitioner’s contradictory statements before the EPO at the very least “significantly weaken and undermine the credibility of Petitioner’s case”).

2. The High Degree of Similarity Between Species Supports Written Description

Petitioner also asserts that PO “cannot ‘make up for’ the absence of disclosure of recombinantly produced *Limulus polyphemus* Factor C and ***extrapolate*** that protein’s claimed residual activity function based on information about other species

⁵ PO maintains its right to pursue an appropriate remedy under 37 C.F.R. § 42.11(d)(2).

of horseshoe crab.” Reply at 11 (emphasis in original). Not only does this argument run afoul of Petitioner’s obviousness attack, *see* Section III, *infra*, but it also again contradicts arguments Petitioner made in the Opposition.

Specifically, in the Opposition, Petitioner identified a reference D5 (Ex. 1032) related to a recombinant Factor C from *Carcinoscorpius rotundicauda* produced in an insect cell. Ex. 1048 ¶¶ 102-103. Petitioner noted that this recombinant Factor C is “shown to be capable of detecting endotoxin” and then argued that a POSA would “have carried out the teaching of D5 as it regards *Limulus polyphemus* because this Factor C would be *expected to exhibit the ‘full biological activity’* of this ‘extremely sensitive’ and well-known endotoxin detecting agent.” *Id.* ¶¶ 112, 114. Petitioner thus “extrapolate[d]” based on the activity of one species of Factor C (*C. rotundicauda*) expressed in an insect cell to argue *Limulus polyphemus* Factor C would also have “full biological activity.”

Petitioner’s argument also implies working examples are necessary, which contravenes black letter law. *See, e.g., Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 127 F.4th 896, 916 (Fed. Cir. 2025) (“There is *no rigid requirement that the disclosure contain ‘either examples or an actual reduction to practice’*”).

As explained in PO’s Response, given the knowledge in the art, including the public deposits and reported high degree of similarity between the small species of horseshoe crabs (only 4 species), a POSA would have expected that functional

activity, such as claimed residual activity, would be maintained across species such that the residual activity data for *Tachypleus tridentatus* in the '767 Application provides adequate written description support. Paper 26 at 11-30.⁶

BASF Plant Sci., LP v. Commonwealth Sci. & Indus. Rsch. Organisation, is instructive. 28 F.4th 1247, 1265 (Fed. Cir. 2022). In *BASF*, the Federal Circuit affirmed written description support existed for claims directed to producing LC-PUFAs in a specifically claimed species of plant cells—canola—despite the specification lacking a working example of production in that species. *Id.* at 1264-1268. Much like the facts here where the '767 Application identifies *Limulus polyphemus* Factor C as an embodiment of the invention, Paper 26 at 26-27, the specification in *BASF* identified canola as an embodiment of the invention. 28 F.4th at 1264-1268. While the specification in *BASF* did not include an example of using canola to produce LC-PUFAs, as the Court explained, “actual reduction to practice is not a requirement of possession.” *Id.* at 1267-1268.

Moreover, the Court noted the specification’s working examples of another species (*Arabidopsis*) supported a holding of adequate written description for the

⁶ Notably, in the Opposition, Petitioner conceded a “high level of identity” existed between the cDNA encoding the *Limulus* Factor C and the cDNA sequence encoding *T. tridentatus*. Ex. 1048 ¶ 88.

different canola species because substantial evidence existed that *Arabidopsis* is a reliable model for canola and highly predictive of positive results in canola. *Id.* at 1265-1266. Here, while the '767 Application examples focus on *Tachypleus tridentatus*, as PO and its expert explain, given the high similarity between the species, a POSA would have expected residual activity to be maintained across species. Paper 26 at 21-24. Indeed, in the Opposition, Petitioner argued in a paper it submitted on **November 21, 2025** that D1 (same specification as the '767 Patent, *see* n.4, *supra*) highlighted that low susceptibility to activity inhibition by ions may be ***expected for a recombinantly produced Factor C from any source*** including *Limulus polyphemus*. Ex. 2099 ¶ 46.

3. Petitioner's Additional Arguments Do Not Support its Written Description Attack

First, Petitioner argues an alignment sequence comparison performed by PO's expert is "fatal to PO's case" because it uses post-December 2013 *Limulus polyphemus* Factor C sequence information. Reply at 9-10. But Petitioner's argument misses the mark. PO's expert provides detailed analyses and support in the art for his assertion residual activity would be maintained across species. *See, e.g.*, Ex. 2038 ¶¶ 85-88, 90-91, 94. The sequence alignment analysis merely confirms the highly similar protein sequences already known. *See, e.g., id.* ¶ 90-91, 94, 99-102.

Moreover, as Petitioner's expert provided unsupported speculation that sequence differences between species were *non-conservative*, thus *potentially* giving rise to changes in functional activity, Paper 14 at 22 (citing Ex. 1002 ¶ 94), the sequence analysis performed by PO's expert provides clear evidence rebutting this speculation. Ex. 2038 ¶ 97 (“[T]he *functional domains are very highly conserved between species*.”); see also *id.* ¶¶ 91-98.⁷

Second, any argument by PO that common structural features are required to demonstrate written description support fails. Reply at 11-13. As explained in PO's Response, claim 21 presents a *narrow* claim directed to (i) Factor C from a *one species* of horseshoe crab (*Limulus polyphemus*); (ii) expressed from a specific cell (HEK293); and (iii) meeting a minimum residual activity threshold in specifically claimed salt solution concentrations. Paper 26 at 25.

⁷ Petitioner's reliance on *Brita LP v. Int'l Trade Comm'n*, is misplaced. 156 F.4th 1326 (Fed. Cir. 2025). In *Brita*, the claims covered “any filtration media type with activated carbon.” The Court did not rely on the lack of working examples to affirm lack of written description but instead noted critical facts, such as the patent's discussion of “disadvantages” of other filter media and the inventors' admissions “they did not create non-carbon block filters.” *Id.* at 1332-1334.

Petitioner's arguments again hinge on it incorrectly analyzing claim 21 as a broad genus claim requiring disclosure of representative species or common structural features, Reply at 12-13, and does not address PO's arguments that the specification provides "sufficient 'blaze marks'" to find written description support exists. Paper 26 at 25-27.

Finally, Petitioner asserts statements in the '498 PCT (Ex. 1005) "undermine" PO's arguments in its Response that sequencing *Limulus polyphemus* Factor C was routine. Reply at 4-5. Not so. As discussed in PO's Response, although the inventors of the '498 PCT may have been the first to take the necessary steps in reality to acquire the full-length cDNA sequence for *Limulus polyphemus* Factor C (Ex. 1005 at [0017]⁸), other skilled artisans had the knowledge and means to do so as well. Paper 26 at 28-29. The statements that Petitioner points to in the '498 PCT do not undermine this conclusion.

Indeed, Petitioner cites paragraphs from the '498 PCT that are not specific to Factor C, but instead more generally discuss "proteins and genes." These paragraphs

⁸ The US Publication of the '498 PCT states the "present inventors were successful in the *acquisition* of full-length cDNAs encoding all protein factors involved in the clotting mechanism of *Limulus polyphemus*." Ex. 1052 at [0025].

also do not state a POSA would not have had the means to sequence *Limulus polyphemus* Factor C:

- “[I]n *Limulus polyphemus*, **the proteins and their genes** involved in the mechanism of coagulation caused by endotoxin have not been completely identified structurally or functionally.” Reply at 4-5 (citing Ex. 1005 ¶¶ 0009-10).
- “[C]omplete identification of these **proteins and genes** in terms of both structure and function has not been achieved . . . not been possible to accurately determine the full-length sequence structure, expression, and function **of these proteins and genes**.” Reply at 5-6 (citing Ex. 1005 ¶ 12)⁹.
- “The full-length sequences of **all proteins and genes** involved in the coagulation mechanism of *Limulus polyphemus* have not yet been elucidated.” Reply at 5 (citing Ex. 1005 ¶ 13).

Thus, Petitioner’s assertion that PO has taken positions in this proceeding that contradict the ’498 PCT fails.

⁹ Notably, Petitioner does not quote the entirety of paragraph 12 of the ’498 PCT on page 6 of its Reply but instead misleadingly truncates the quote to cut out the reference to “proteins **and genes**.” Ex. 1005 ¶ 12.

a. Petitioner's Inconsistent Positions Undercut Its Credibility and Arguments Regarding the '498 PCT

Not only does Petitioner fail to demonstrate PO has taken inconsistent positions in the '498 PCT, but Petitioner conveniently ignores its numerous inconsistent arguments presented in this proceeding versus those it presented before the EPO in the Opposition it filed. Paper 26 at 29-31.

For example, while here Petitioner relies on paragraph 12 of the '498 PCT to support its argument that constructing and expressing the *Limulus polyphemus* Factor C coding sequences was not routine in 2013, Reply at 5-6, in the Opposition it argued the contrary, stating “the mere statement in par. [0012] . . . which alleges that the determination of this [*Limulus polyphemus*] sequence ‘*could not be achieved by general techniques*’ **is entirely unsupported.**” Ex. 1048 ¶ 75; *see also id.* ¶ 35 (stating paragraph [0012] “is very generic and entirely unsupported”); *see also id.* at 9, n.2 (“[T]here were **no** unforeseen technical difficulties in determining the [*Limulus polyphemus*] sequence”).

Petitioner's inconsistent positions taken here should thus be viewed with extreme skepticism, if not disregarded.¹⁰ *See Provepharm*, 2019 WL 2865314, at *15.

¹⁰ Petitioner's reliance on McClymont does not support its argument that it was not routine to sequence *Limulus polyphemus*, Reply at 6-7, 19-20, particularly given

Accordingly, the Board should find that adequate written description support exists.

B. The '767 Application Enables the Full Scope of the Claim

Petitioner again asserts that claim 21 recites a broad range of residual activity values but does not explain how a POSA could produce proteins at the lower end middle points, or highest points of the range. Reply at 20-21. Petitioner's arguments ignore PO's Response that explained a POSA would have understood the residual activities in claim 21 as simply requiring the minimum threshold of relative reactivity in different salt solutions (*i.e.*, sodium citrate and magnesium sulfate) that must be present for the recombinantly produced Factor C to exhibit the inventive concept: low susceptibility to inhibition of activity by an ion. It would not be understood as requiring a "wide claimed range" of residual activities as Petitioner argues. Paper 26 at 34.

Given this proper interpretation of the invention, undue experimentation would not have been required to practice the full scope of claim 21, and Petitioner

Petitioner's Opposition arguments to the contrary. Moreover, as McClymont is a PhD thesis, McClymont herself is not a POSA under either parties' definition that her work should also be viewed with skepticism. Paper 26 at 10-11.

cannot demonstrate the '767 Application does not enable the claim. Paper 26 at 31-44.

III. CLAIM 21 IS NOT OBVIOUS

A. If Mizumura and the '498 PCT are Considered Prior Art, Petitioner Failed to Meet its Burden to Demonstrate Unpatentability of Claim 21 (Ground 1)

Petitioner asserts “PO does not argue that the combined teachings of Mizumura and the '498 PCT fail to disclose all of the limitations of claim 21.” Reply at 22. Not so. PO expressly argued in its Response that “Petitioner has failed to demonstrate anything in the prior art disclosing the claimed residual activity for the specifically claimed *Limulus polyphemus* Factor C expressed in HEK293 cells.” Paper 26 at 45-46.

Petitioner also reiterates its conclusion that a POSA would have had a reasonable expectation of success in generating the claimed *Limulus polyphemus* Factor C in HEK293 cells with the claimed residual activity. But Petitioner’s reasonable expectation of success theory cannot be squared with its assertions relating to the lack of Section 112 support for the claims.

Indeed, Petitioner cannot argue as it does in Reply that PO “cannot ‘make up for’ the absence of disclosure of recombinantly produced *Limulus polyphemus* Factor C and *extrapolate* that protein’s claimed residual activity function based on information about other species of horseshoe crab” to support a Section 112 attack,

Reply at 11, but then turn around and argue the same type of extrapolation can be performed to support a reasonable expectation of success in achieving the claimed residual activity with *Limulus polyphemus* Factor C based on the prior art's disclosure of residual activity values for *Tachypleus tridentatus*.

Moreover, Petitioner devotes over five pages of its Reply to arguing that “a POSA would not have leaped to the conclusion that two **recombinantly** produced proteins would have similar properties with respect to residual activity.” Reply at 14; *see also id.* at 13-19. Indeed, Petitioner expressly states “a POSA **would not do** what PO insists they would—predict the residual activity in very specific ion concentrations of a new recombinantly-produced protein (from *Limulus polyphemus* based on the reported residual activity of an entirely different species of protein.” *Id.* at 16-17. Petitioner further states “a POSA would have agreed with Dr. Jain that any predictions about residual activity in recombinant *Limulus polyphemus* Factor C **would have been pure speculation.**” *Id.* at 18-19.

These arguments directly undermine Petitioner's obviousness case. The prior art says **nothing** about the residual activity of recombinantly-produced *Limulus polyphemus* Factor C in the very specifically claimed ion concentrations, so Petitioner is forced to rely on residual activity data for recombinantly-produced *Tachypleus tridentatus* Factor C described in Mizumura. Petitioner cannot, as it does, argue a POSA would not predict residual activity for recombinantly produced

Factor C of one species based on data from another recombinantly produced Factor C from another species but then also argue a reasonable expectation of success exists. Paper 2 at 57-60. These arguments simply cannot be reconciled.

Because of these inconsistent positions, Petitioner's reasonable expectation of success arguments should be rejected. Petitioner has thus failed to demonstrate a reasonable expectation of success to support its obviousness argument. *See Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1348 (Fed. Cir. 2021).

B. If Mizumura and McClymont were Considered Prior Art, Petitioner Has Failed to Meet its Burden to Demonstrate Unpatentability of Claim 21 (Ground 2)

For the same reasons as discussed in Ground 1, incorporated here, Petitioner failed to meet its burden to demonstrate a reasonable expectation of success in modifying Mizumura in view of McClymont to arrive at the claimed invention.

As such, Petitioner has failed to meet its burden to show that claim 21 of the '318 Patent is unpatentable under either Ground 1 or Ground 2.

IV. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS EXIST

Contrary to Petitioner's assertions, secondary considerations of non-obviousness also exist to support the patentability of claim 21. Paper 26 at 49-56.

First, Petitioner argues the data in the Mizumura Declaration is "irrelevant" because it provides data in CHO DG44 cells, not the claimed HEK293 cells. Reply at 24-25. Not so. While the Mizumura Declaration provides data in CHO cells, the

data is for the ***claimed*** *Limulus polyphemus* Factor C. Paper 26 at 51-53. PO cites to this data to demonstrate that, as compared to the closest prior art (Mizumura) that uses non-claimed *Tachypleus tridentatus* Factor C, the claimed *Limulus polyphemus* Factor C exhibits unexpectedly superior residual activity. *Id.*

Second, Petitioner argues that opinions by PO’s expert regarding data in D19 (Ex. 2033) “should be given no weight.” Reply at 26. As PO explains, however, the data in Ex. 2033 demonstrates unexpectedly superior residual activities for *Limulus polyphemus* Factor C in HEK293 cells as compared to the closest prior art. Paper 26 at 53-56. Notably absent from Petitioner’s critique of this data is its admission that the data in D19 appears to come from ***Petitioner’s own experimental work***. Compare Ex. 2033 at 4 with Ex. 2034 at Fig. 15, [0042].

Petitioner’s arguments are unavailing. Thus, the claimed invention exhibits unexpected results, which weighs in favor of finding claim 21 of the ’318 Patent not unpatentable as obvious.

V. CONCLUSION

For the reasons discussed above, the Board should maintain the patentability of claim 21 of the ’318 Patent.

Respectfully Submitted,

Dated: April 13, 2026

/ Alexander B. Stein /
Alexander B. Stein, Reg. No. 71,397

CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the foregoing Patent Owner Sur-Reply complies with the applicable type-volume limitations of 37 C.F.R. § 42.24(b)(2). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a)(1), this Sur-Reply, including footnotes, contains 3,630 words, as counted by the word count function of Microsoft Word. This is less than the limit of 5,600 words as specified by 37 C.F.R. § 42.24(c)(4).

Respectfully Submitted,

Dated: April 13, 2026

/ Alexander B. Stein /
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), lead counsel for Patent Owner hereby certifies that on April 13, 2026, a copy of this PATENT OWNER’S SUR-REPLY was served via the email correspondence address of record for Petitioner’s counsel of record:

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