

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHARLES RIVER LABORATORIES, INC.,
Petitioner,

v.

SEIKAGAKU CORPORATION,
Patent Owner.

IPR No. IPR2025-00440
Patent No. 11,236,318

**PETITION FOR INTER PARTES REVIEW
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.1 et seq**

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APPENDIX LISTING OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 11,236,318 (“the ’318 patent”)
1002	Declaration of Siddhartha Jain, Ph.D., PMP (“Jain”)
1003	Curriculum Vitae of Dr. Siddhartha Jain, Ph.D., PMP
1004	Prosecution History for U.S. Application No. 16/399,386
1005	International Patent Publication No. WO 2018/074498 A1
1006	U.S. Patent Application No. 14/650,767, as filed June 9, 2015
1007	Muta et al., “Limulus Factor C. An endotoxin-sensitive serine protease zymogen with a mosaic structure of complement-like, epidermal growth factor-like, and lectin-like domains,” <i>J Biol Chem.</i> 1991 Apr 5; 266(10):6554-61.
1008	Gan et al., “Analysis of Protein Sequence/Structure Similarity Relationships,” <i>Biophys J.</i> 2002 Nov; 83(5):2781-91.
1009	U.S. Patent Application Publication No. 2015/0307864
1010	Karen McClymont, Ph.D. Thesis, submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy from the University of Glasgow, Institute of Molecular, Cell and Systems Biology College of Medical, Veterinary and Life Sciences, March, 2017.
1011	Transition Certification for U.S. Patent Application No. 15/983,725, filed May 31, 2019.
1012	U.S. Patent No. 5,716,834
1013	Declaration of Dr. Mary K. Bolin
1014	U.S. Patent No. 5,858,706
1015	International Patent Publication No. WO 2000/026366 A1
1016	Iwanaga, Sadaaki, “Biochemical principle of <i>Limulus</i> test for detecting bacterial endotoxins,” <i>Proc. Jpn. Acad., Ser. B. Phys Biol Sci.</i> 2007 May; 83(4):110-9.
1017	RESERVED
1018	RESERVED
1019	Japanese Priority Document JP2012-269840 (certified translation, plus original)
1020	U.S. Application No. 14/650,767, addition to PCT specification
1021	Higdon, R. et al., “Modeling sequence and function similarity between proteins for protein functional annotation,” <i>Proc Int Symp High Perform Distrib Comput</i> ; 2010: 499–502.

Exhibit	Description
1022	Tokunaga, F., et al. "Further studies on lipopolysaccharide-sensitive serine protease zymogen (Factor C): Its isolation from <i>Limulus polyphemus</i> hemocytes and identification as an intracellular zymogen activated by α -chymotrypsin, not by trypsin," <i>J. Biochem.</i> 1991 Jan; 109(1):150-7.
1023	Levin, J., Bang, F., "The role of endotoxin in the extracellular coagulation of <i>Limulus</i> blood," <i>Bulletin of John's Hopkins Hospital.</i> 1964 Sep: 115:265-74.
1024	Walls, E. et al, The Horseshoe Crab, <i>Limulus polyphemus</i> : 200 Million Years of Existence, 100 Years of Study, <i>Reviews in Fisheries Science.</i> 2002; 10(1):39-73.
1025	Carmichael, R., et al., "Changing Global Perspectives on Horseshoe Crab Biology, Conservation, and Management," Springer, Ch. 29: "Biotechnology Efforts to Conserve Horseshoe Crabs Through the Development of Recombinant Factor C-Based Endotoxin Test" pp. 501-512 (2015).
1026	Dwarakanath et al., "Recombinant COS-1 cells express <i>Carcinoscorpius rotundicuada</i> Factor C," <i>Biotechnology Letters.</i> 1997 April; 19(4):357-361.
1027	Wang, J. et al., "Functional expression of full length <i>Limulus</i> Factor C in stably transformed Sf9 cells," <i>Biotechnology Letters.</i> 2001; 23:71-76.
1028	Ding et al, "A new era in pyrogen testing," <i>Trends in Biotechnology.</i> 2001 Aug; 19(8):277-81.
1029	U.S. Appln. No.: 14/650,767, "Novel Recombination Factor C and Method for Producing the Same, and Method for Measuring Endotoxin," Declaration Under 37 C.F.R. § 1.132, Feb. 22, 2018.
1030	Barrabes, S. et al., "Effect of sialic acid content on glycoprotein p/ analyzed by two-dimensional electrophoresis," <i>Electrophoresis.</i> 2010 Sep; 31(17):2903-12.
1031	Palomares, L.A., "Production of Recombinant Proteins: Challenges and Solutions," From: <i>Methods in Molecular Biology</i> , vol. 267: <i>Recombinant Gene Expression: Reviews and Protocols</i> , Second Edition Edited by: P. Balbás and A. Lorence © 2004 Humana Press Inc., Totowa, NJ, pp. 15-51
1032	U.S. Patent No. 6,645,724
1033	Mizumura, H., et al., "Genetic engineering approach to develop next-generation reagents for endotoxin quantification," <i>Innate Immunity.</i> 2017 Feb; 23(2):136-146.

Exhibit	Description
1034	Ding et al., “Expression of full length and deletion homologues of <i>Carcinoscorpius rotundicauda</i> Factor C in <i>Saccharomyces cerevisiae</i> : immunoreactivity and endotoxin binding,” <i>Journal of Endotoxin Research</i> . 1997; 4(1): 33-43.
1035	International Patent Publication No. WO 2014/092079 A1 (“the ‘082 PCT”)
1036	Wang et al., “Modular Arrangement and Secretion of a Multidomain Serine Protease,” <i>J Biol Chem</i> . 2002 Sep 27; 277(39):36363-72.
1037	Marengo-Rowe, Alain, J., “Structure-function relations of human hemoglobins,” <i>Proc (Bayl Univ Med Cent)</i> 2006 Jul; 19(3):239–245.
1038	Sekiguchi, K. and Shuster, C.N., “Limits on the Global Distribution of Horseshoe Crabs (Limulacea): Lessons Learned from Two Lifetimes of Observations: Asia and America,” <i>Biology and Conservation of Horseshoe Crabs</i> , 2009.
1039	Hossler et al., “Optimal and consistent protein glycosylation in mammalian cell culture,” <i>Glycobiology</i> . 2009 Sep; 19(9):936-4.

MANDATORY NOTICES

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

Petitioner Charles River Laboratories, Inc. (“Charles River” or “Petitioner”) is the Real Party-in-Interest.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

A decision in this proceeding could affect or be affected by the following:

1. United States Patent & Trademark Office

The application from which U.S. Patent No. 11,236,318 issued is a continuation of U.S. Patent Application No. 15/983,725 (U.S. Patent No. 10,982,202), filed May 18, 2018, which is a continuation of U.S. Patent Application No. 14/650,767 (U.S. Patent No. 10,144,923), filed on June 9, 2015, which is a National Stage Entry of PCT/JP2013/083082, filed on December 10, 2013.

The following U.S. Patent applications claim benefit of priority to U.S. Patent No. 11,236,318: U.S. Patent Application No. 17/554,128, filed December 17, 2021, and U.S. Patent Application No. 18/346,420 (now U.S. Patent No. 11,959,109), filed July 3, 2023.

2. United States Patent Trial and Appeal Board (“PTAB”)

There are no proceedings before the PTAB that could affect or be affected by a decision in this proceeding.

C. Counsel and Service Information – 37 C.F.R. §§ 42.8(b)(3) and (4)

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A power of attorney is submitted with the Petition. Counsel for Petitioner consents to service of all documents via electronic mail.

I. INTRODUCTION

The '318 patent (EX1001) is directed to recombinantly-produced Factor C proteins—enzymes useful in detecting the presence of biologically harmful endotoxins that contaminate medical products. The sole challenged claim 21 recites recombinantly-produced horseshoe crab Factor C proteins from the *Limulus polyphemus* species of horseshoe crab, defined by a particular function—a “residual activity” falling within a range above low claimed thresholds. As demonstrated in this Petition, the full scope of claim 21 is neither described nor enabled by any application in the '318 patent's priority chain and is therefore entitled to an effective filing date no earlier than the April 30, 2019 actual filing date of the '318 patent. When afforded this correct priority date, claim 21 is obvious over the prior art.

Challenged claim 21 of the '318 patent recites Factor C proteins from the *Limulus polyphemus* species of horseshoe crab that are recombinantly produced in HEK293 cells and exhibit a “residual activity” function relating to the protein's ability to detect endotoxin in the presence of otherwise inhibitory ions.

Recombinant production involves using the genetic information for a particular protein (either the gene sequence or the amino acid sequence of that protein), and “programming” a host cell (like HEK293) with this information so that the host cell produces (or “expresses”) the protein *in vitro* (in a lab).

Despite claiming Factor C proteins from a particular species of horseshoe crab, made in a particular way, and having a particular function, the priority document for the '318 patent ***never discusses or provides a single example*** of any recombinantly produced Factor C protein from *Limulus polyphemus*—the species native to North America—let alone any example meeting the functional requirements of that claim. Instead, this priority document (the representative “’767 Application”) provides gene and amino acid sequences for “preferred” Factor C proteins derived from two entirely different, unclaimed, and geographically segregated crab species—*Tachypleus tridentatus* (native to Japan) and *Carcinoscorpius rotundicauda* (native to Singapore).

Nor does the '767 Application provide any common structural features of such proteins across species that would result in possession of the requisite residual activity for recombinant *Limulus polyphemus* Factor C proteins across the full scope of claim 21, in the absence of the sequences themselves. To the contrary, while the inventors theorized in the '767 Application that increased residual activity was linked to the addition of a post-translation (α -2,3)-linked terminal sialic acid on Factor C proteins when such were recombinantly expressed in mammalian cells, they explicitly abandoned this theory during prosecution, admitting that it did not hold for the claimed *Limulus polyphemus* species. Without sequence information, any experimental example, or any accurate common

structural feature shared by these proteins driving their residual activity, the '318 patent inventors were not in possession of the full scope of functional proteins encompassed by claim 21.

The '767 Application does not (and could not) disclose—as of 2013—any example of the claimed recombinant *Limulus polyphemus* Factor C protein because it is undisputed that as of the December 10, 2013 filing of that disclosure, the full gene and amino acid sequences for the *Limulus polyphemus* species of horseshoe crab **were not yet known or disclosed**. Instead, limited and partial amino acid sequence information for *Limulus polyphemus* horseshoe crabs revealed key differences between such sequences and those of different crab species discussed in the '767 Application. Given the well-understood principle that gene and protein sequences between species will vary such that predictions about comparable function are uncertain, persons of ordinary skill in the art (“POSAs”) would not have understood the '318 patent inventors to have adequately described, in the '767 Application, the functionally-claimed *Limulus polyphemus* Factor C proteins of claim 21 in a manner sufficient to have demonstrated their possession of such proteins. In fact, the '318 patent inventors fully admitted this when, on April 26, 2018—more than one year prior to the actual filing date of the '318 patent and over four years **after** its claimed priority date—they published a different and unrelated patent application in which they explained that the “in *Limulus polyphemus*, the

proteins and their genes involved in the mechanism of coagulation caused by endotoxin have not been completely identified structurally or functionally...even though more than 20 years have passed since the report in the genus *Tachypleus*.”¹ EX1005, ¶¶0002-13. The inventors explained that “due to the various differences and diversity of biomolecules depending on the genus and species of horseshoe crab it has not been possible to accurately determine the full-length sequence structure, expression, and function of these proteins and genes using conventional methods.” *Id.* The inventors confirmed, however, that they ***finally*** (allegedly, in 2017) “succeeded in obtaining full-length cDNAs encoding all of the protein factors involved in the coagulation mechanism of *Limulus polyphemus*, something that no one had succeeded in doing for many years...thereby completing the present invention.” *Id.*, ¶0017.

In view of the absence of any disclosure, sequence information, or examples in the '318 patent's priority document of any recombinant Factor C protein falling within the scope of claim 21, in view of known differences in ***partial*** amino acid sequences between *Limulus polyphemus* Factor C proteins and other species of horseshoe crabs, in view of the geographic segregation of these horseshoe crabs, and based on the inventors' own admissions years later that the field had struggled and been unable to sequence, structurally characterize, and recombinantly produce

¹ All emphasis added and internal citations omitted, unless otherwise stated.

recombinant *Limulus polyphemus* Factor C proteins, neither the '767 Application nor any application in the priority chain of the '318 patent provides a sufficient written description of full scope of the purported invention of claim 21. *Billups-Rothenberg, Inc. v. Associated Reg'l & Univ. Pathologists, Inc.*, 642 F.3d 1031, 1037 (Fed. Cir. 2011) (no written description where “[Patentee] did not possess a genetic mutation useful for diagnosing hemochromatosis when it filed its patent application in December of 1994...[which was confirmed by] the **subsequent** discovery of C282Y [gene]....[Patentee] cannot satisfy the written description requirement merely through references to later-acquired knowledge.”).

In addition to failing to describe the full scope of claim 21, the '767 Application also fails to enable a POSA to make and use the full scope of claimed *Limulus polyphemus* Factor C proteins with the claimed residual activity, where that specification provides no examples of any such *Limulus polyphemus* proteins, only a single example of such protein (from a **different** species of crab) falling within the wide claimed range, and no other guidance about how a POSA would achieve the production of recombinant *Limulus polyphemus* Factor C proteins across the full scope of the wide claimed functional range without undue experimentation. Rather, significant experimentation would have been required by a POSA to sequence this unknown protein (which, as the inventors admitted “**has not been achieved**...due to various differences and diversity of biomolecules

depending on the genus or species of horseshoe crab” (EX1005, ¶0012), and then produce and verify recombinant Factor C proteins from the *Limulus polyphemus* crab with the claimed residual activity across the **full scope of claim 21** (where the ’767 Application provided not even one example). Providing merely a wish or plan—or, here, even less—does not enable the full scope of a claim. *Medytox, Inc. v. Galderma S.A.*, 71 F.4th 990, 998-99 (Fed. Cir. 2023) (affirming nonenablement where the “responder rate” limitation had an upper limit of 100% but the specification only disclosed examples of 52%, 61%, and 62%, and no examples approaching the upper limit of 100%—“[A] specification need not always ‘describe with particularity how to make and use every single embodiment within a claimed class,’ it must nevertheless ‘enable the full scope of the invention’...for example by ‘disclosing [a] general quality’ of the class that may ‘reliably enable a [POSA] to make and use all of what is claimed.’”).

Claim 21 is neither described nor enabled by the ’767 Application and should be afforded an effective filing date no earlier than the actual filing date of the ’318 patent (April 30, 2019). Grounds 1 and 2 are therefore based on indisputable post-America Invents Act (“AIA”) 35 U.S.C. § 102(a)(1) prior art.

Ground 1 establishes that claim 21 is obvious over the U.S. Publication of the ’767 Application (**Mizumura**) (EX1009), in view of **the ’498 PCT** (EX1005). Mizumura discloses every limitation of claim 21 except for the gene and amino

acid sequence information for—and recombinant production (in HEK293 cells) of—Factor C from the *Limulus polyphemus* species. However **by 2019**, a POSA would have had access (via at least the '498 PCT) to the then-recent sequence disclosure of *Limulus polyphemus* Factor C. In view of these teachings, a POSA in 2019 would have recognized the scientific advantages of recombinant protein production starting with Mizumura's reported success with the residual activity of recombinant *Tachypleus tridentatus* Factor C. This would have provided a POSA with reason to apply such teachings to the recombinant production of *Limulus polyphemus* Factor C, per the '498 PCT's description of having finally succeeded in making this recombinant protein in a mammalian expression system (EX1005, ¶¶0017), and having demonstrated functional endotoxin detection with the same. *Id.*, ¶¶0181-0183. A POSA would have had a reason to modify Mizumura with the teachings of the '498 PCT and would have reasonably expected to produce a recombinant Factor C protein with a “residual activity” falling within the claimed range.

That two separate publications from Patent Owner, together, render claim 21 obvious as April 30, 2019 is of no help to Patent Owner in establishing an earlier effective filing date. *Ariad Pharms. Inc., v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (“[A] description that merely renders the invention obvious does not satisfy the [written description] requirement.”).

Ground 2 is similar to Ground 1 but relies upon the *Limulus polyphemus* sequence and expression disclosure of the March 2017 Ph.D. Thesis by Karen McClymont (EX1010) instead of the '498 PCT and likewise demonstrates why challenged claim 21 is unpatentable as obvious over the prior art.

II. CERTIFICATION OF STANDING

The '318 patent is available for IPR and Petitioner is not barred or estopped from requesting IPR as to the challenged claim. 37 C.F.R. § 42.104(a).

III. GROUNDS FOR UNPATENTABILITY

The table below identifies the references, applicable claim, and basis for each ground of unpatentability. This Petition is supported by the Declaration of Dr. Siddhartha S. Jain (EX1002) (“Jain”).

Ground Number and Reference(s)		Claim	Basis
1	Mizumura in view of the '498 PCT	21	35 U.S.C. §103 (post-AIA) ²
2	Mizumura in view of McClymont	21	35 U.S.C. §103 (post-AIA)

² During prosecution of parent Application No. 15/983,725 (“the '725 Application”)), Patent Owner filed a “Statement Under 37 C.F.R. § 1.55 or § 1.78 for AIA (First Inventor to File) Transition Applications.” EX1011, 1. The Office examined the '725 Application and all subsequent applications in the priority chain (including the '318 patent) under post-AIA law.

IV. TECHNOLOGY BACKGROUND

The '318 patent relates to endotoxin testing for quality assurance of medical and pharmaceutical products. It claims recombinant Factor C proteins—enzymes sourced from the hemolymph (invertebrate equivalent of blood) of horseshoe crabs which were discovered to undergo a clotting reaction in the presence of a harmful bacterial substance known as endotoxin. *See* EX1001, 1:27-54. This clotting phenomenon has since been relied upon by the biomedical industry to generate tests for the detection and quantitation of endotoxin that may have contaminated medical products. *Id.* 1:41-54; Jain, ¶¶35-36.

The gene and amino acid sequences for Factor C for *Tachypleus tridentatus* and *Carcinoscorpius rotundicauda* species of horseshoe crab were known prior to the earliest claimed priority date of the '318 patent. EX1007, 6556³; EX1012, 2:64-3:10. The sequences encoding full-length Factor C for the horseshoe crab species *Limulus polyphemus*, however, had **not** been described until much more recently. *See* EX1010, 159-160; EX1005, 49-57 (SEQ ID NOS. 1-4); Jain, ¶¶40-41.

³ The Declaration of Dr. Mary K. Bolin (EX1013) authenticates EX1007-1008, EX1016, EX1021-1025, EX1028, EX1030-1031, EX1033-1034, EX1036-1039.

In the decade leading up to the earliest effective filing date of the '318 patent, and in view of the labor-intensive methods required to obtain Factor C protein from horseshoe crabs directly, many scientists turned to the recombinant expression of Factor C as an alternative source of this protein. Jain, ¶¶39; EX1014, Abstract, 2:66-3:43; EX1015, 25-27, 29-30.

V. THE '318 PATENT

The '318 patent discusses the production of recombinant Factor C protein from several mammalian cell lines. EX1001, 18:25-54. According to the specification, expression of Factor C from known industrial production strains, including Chinese Hamster Ovary ("CHO"), purportedly solves the problem of ion interference with the Factor C signaling cascade that limits endotoxin recovery (thus underestimating endotoxin levels). EX1001, 3:12-18 ("[R]ecombinant horseshoe crab Factor C can be produced by use of human cells or Chinese hamster cells as host cells, and that endotoxin can be measured by use of the thus-produced recombinant Factor C while reaction inhibition in the presence of a salt (ion) is mitigated."), 35:26-43; Jain, ¶¶38, 42.

This concept of "reaction inhibition in the presence of a salt (ion) is mitigated" is captured in the '318 patent claims by the term "residual activity" which the '318 patent says is a measurement of the activity of a reconstituted Factor C cascade in detecting a given amount of endotoxin in an ion solution

relative to the activity of the reconstituted cascade in detecting the same amount of endotoxin in water. *Id.*, 18:8-15. The inventors tested the residual activity of *Tachypleus tridentatus* Factor C protein recombinantly produced via several expression systems and exposed to particular concentrations of various ionic solutions. EX1001, 34:39-35:43, FIG. 7; Jain, ¶¶37, 43-44.

A. The Challenged Claim

Challenged claim 21 recites:

A horseshoe crab Factor C protein having activity of Factor C,
wherein the horseshoe crab is *Limulus polyphemus*, and

wherein the horseshoe crab Factor C protein is produced through
being recombinantly expressed from a Human Embryonic Kidney
(HEK) 293 cell, and

wherein the Factor C protein exhibits a residual activity of at least one
selected from the group consisting of:

- (1) 10% or higher in the presence of 21 mM sodium citrate; and
- (2) 15% or higher in the presence of 16 mM magnesium sulfate.

B. Prosecution History

Patent Owner filed the '386 Application with 18 claims. Original claim 1 recited:

1. A horseshoe crab Factor C protein having activity of Factor C,
wherein the horseshoe crab is selected from the group consisting of
Tachypleus tridentatus, *Limulus polyphemus*, and *Carcinoscorpius*

rotundicauda, and wherein the horseshoe crab Factor C protein is produced through being recombinantly expressed from a Chinese Hamster Ovary (CHO) DG44 cell or HEK cell.

EX1004, 515. This claim recited nothing about the “residual activity” of the horseshoe crab Factor C. Jain, ¶¶50-52.

Claim 2 recited Factor C proteins by explicitly disclosed sequences or sequences “having 90% of higher sequence identity to” such disclosed sequences. Claim 2 also recited “wherein the Factor C protein exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate.” *Id.*, 515-16. Claim 2 said nothing about proteins of particular species of horseshoe crabs. Jain, ¶52.

Claim 11 recited, “The Factor C protein according to claim 2, which contains (α -2,3)-linked terminal sialic acid in a greater amount, as compared with a corresponding native horseshoe crab Factor C protein and/or a corresponding horseshoe crab Factor C protein recombinantly expressed using Sf9 as a host cell” (hereafter, the “Greater Sialic Acid Limitation”). *Id.*, 517. Jain, ¶52.

In the first Office Action on the merits (June 30, 2020), the Examiner rejected claims 2-9, 12, and 13 for inadequate written description. EX1004, 371-76. The Examiner asserted that the rejected claims recited a broad genus with insufficient disclosure of representative species and a failure to link the “residual activity” function claimed with some structural feature, namely the Greater Sialic

Acid Limitation found in other pending claims. *Id.*, 375-76. The Examiner also rejected claims 1-13 as obvious. *Id.*, 376-84. Jain, ¶53.

In response, Patent Owner amended claim 2 to incorporate the Greater Sialic Acid Limitation of claim 11 (not rejected under § 112). *Id.*, 227-28. Patent Owner also submitted a September 9, 2020 declaration from first-named inventor Dr. Hikaru Mizumura who testified that the inventors had “succeeded in cloning cDNA Factor C from *Limulus polyphemus* (=LpFC) hemocyte” and cited U.S. Pub. No. 2019/0241629, the **2019** U.S. Publication of the ’498 PCT in which Patent Owner claimed separately to have finally invented recombinant *Limulus polyphemus* Factor C protein. *Id.*, 245-46. Based on this ***newly determined*** sequence data for *Limulus polyphemus* horseshoe crabs, Dr. Mizumura testified to recently uncovering the relative identity between the amino acid sequences of *Limulus polyphemus*, *Tachypleus tridentatus* and *Carcinoscorpius rotundicauda*. *Id.*, 245-48.

The Examiner subsequently withdrew the § 112 rejection but maintained the § 103 rejection as to pending claims 1-10, 12, 13, and 19. *Id.*, 185-202. Patent Owner then amended ***claim 1*** to now ***also*** recite the Greater Sialic Acid Limitation. *Id.*, 168. Patent Owner submitted another declaration by Dr. Mizumura, this time alleging that the present invention provides “unexpected superior results over” the cited prior art. *Id.*, 149-53. Jain, ¶55-56.

The Examiner again rejected claims 1-9, 12, 13, and 19-23 as obvious over the cited prior art. *Id.*, 101-15. In response, on August 24, 2021, Patent Owner added new claim 24 (issued claim 21) which now ***did not require*** the presence of (α -2,3)-linked terminal sialic acid despite the multitude of earlier amendments adding this limitation to resolve the Examiner's written description rejection. *Id.*, 73. Patent Owner filed a third Inventor Declaration by Dr. Mizumura, again alleging unexpectedly superior results achieved with the claimed Factor C. *Id.*, 82-87. In a striking about-face, however, Patent Owner ***and*** Dr. Mizumura conceded that "superior salt tolerance can be reproduced ***irrespective of*** presence of (α -2,3)-linked terminal sialic acid, at least for *Limulus* Factor C recombinantly produced by using HEK 293 cell as a host." *Id.*, 77, 86; Jain, ¶¶57-59.

In a subsequent Examiner-Initiated Interview, the Examiner proposed amendments to claims 14 and 18, which were authorized by Patent Owner. *Id.*, 25. The Examiner thereafter allowed the claims. *Id.*, 14; Jain, ¶60.

VI. DISCRETIONARY DENIAL IS NOT APPROPRIATE.

A. 35 U.S.C. § 325(d)

The instant Petition presents new and non-cumulative art and arguments relative to prosecution of the '318 patent. To the extent any such art or argument is deemed similar to or cumulative of the art considered during prosecution, this Petition establishes that the Office materially erred in allowing the challenged

claims over the art previously presented. *See Advanced Bionics v. MD-EL*, IPR2019-01469, Paper 6, at 7-9 (Feb. 13, 2020) (precedential).

1. Step 1: The Petition Advances Art and Arguments Not Previously Considered.

a. The Written Description Argument Made in This Petition Was Not Previously Considered Against Claim 21.

Ground 1 of this Petition argues that the alleged priority documents do not support a claim to the genus of Factor C proteins encompassed by claim 21 and that intervening art between the incorrect priority date and actual filing date is applicable. *See* Sections IX and XI, *infra*.

During prosecution of the '318 patent (the '386 Application), the Examiner rejected then-pending claims 2-9, 12, and 13 under § 112 because those claims were “drawn to or recite a Factor C protein having activity of Factor C, wherein the Factor C protein comprises an amino acid sequence selected from [many, including that for *Tachypleus tridentatus*] and having activity of Factor C, wherein the Factor C protein is produced through being recombinantly expressed from a Chinese Hamster Ovary (CHO) DG44 cell or HEK cell, and wherein the Factor C protein exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate,” which were not described in the specification. EX1004, 371-76.

To his credit, the Examiner recognized the vast genus of Factor C proteins encompassed by such claims and determined that the minimal representative

species disclosed in the '386 Application lacked any structure-function correlation and were not sufficiently representative of the genus. *Id.*, 375-76. However, this determination is different from the Petition's written description challenge to claim 21's priority date in two significant respects.

First, the genus defined by the claim considered by the Examiner (as-filed claim 2) *did* encompass at least some representative species (the sequences listed in that claim encompassed the *Tachypleus tridentatus* species), which—without conceding that such species were representative of the entire genus claimed—is *not* the case for any argument made in this Petition. *See* Section IX, *infra*.

Second, in response to the Examiner's rejection, the Patent Owner *amended* the rejected claims to recite the Greater Sialic Acid limitation as a purported common structural feature of the claimed genus, which is *not* recited in challenged claim 21. EX1004, 227-228, 234. The Examiner withdrew the written description rejection responsive to this claim amendment. *Id.*, 185. As discussed above, challenged claim 21 was added much later at the *end* of prosecution—on August 24, 2021—after a series of rejections to the obviousness of the then-pending claims. *Id.*, 73. The Examiner (should have, as discussed in Section VI.A.2, *infra*, but) did not make any further rejections based on the written description.

In view of these differences between pending (and amended) claim 2 and challenged claim 21, the Examiner's written description rejection against claim 2 is

not the same or substantially the same argument advanced in this petition regarding why ***claim 21*** is not sufficiently described by the '767 Application and therefore is not entitled to an effective filing date earlier than its actual filing date.

b. The Enablement Argument Made in This Petition Was Not Previously Considered Against Claim 21.

The Examiner did not reject any pending claims of the '386 Application for inadequate enablement. Accordingly, the enablement arguments advanced in this Petition do not present the same or substantially the same art or argument previously presented under *Advanced Bionics*.

c. The Art Relied Upon in the Two Grounds of this Petition Was Not Previously Considered Against Claim 21.

Neither Mizumura, nor the '498 PCT, nor McClymont were of record or cited or applied during prosecution of the '318 patent, where the Examiner made no substantive determination about whether the '318 patent was entitled to an earliest effective filing date of December 10, 2012. *See e.g.*, EX1004, 369.

2. Step 2: The Office Committed Material Error.

a. The Office Erred In Failing to Reject Claim 21 For Lacking Written Description Support.

As noted above, while the Examiner rejected claims 2-9, 12, and 13 as lacking adequate written description support and only dropped this rejection when these claims were amended to recite the Greater Sialic Acid Limitation, he never revisited this § 112 deficiency when claim 24 was added ***without*** the Greater Sialic

Acid limitation. The Examiner materially erred by failing to re-lodge the prior § 112 rejection when Patent Owner introduced a claim that did not contain the amendment previously made to overcome the Examiner's initial rejection.

In addition, the Mizumura declaration submitted in response to the Examiner's § 112 rejection relied upon gene and amino acid sequence information for the *Limulus polyphemus* species of horseshoe crabs that was ***not known or disclosed*** as of the claimed priority date of the '318 patent. EX1004, 245 ("We have succeeded in cloning cDNA encoding Factor C from *Limulus polyphemus*."). To the extent the Examiner relied upon such later-acquired information to establish the inventors' possession of the functionally-claimed recombinant *Limulus polyphemus* Factor C proteins as of December 10, 2012, such was material error. *Billups-Rothenberg, Inc.*, 642 F.3d at 1037 ("[Patentee] cannot satisfy the written description requirement merely through references to later-acquired knowledge."); *Biogen Int'l GMBH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1342-44 (Fed. Cir. 2021) (no written description—"[E]vidence illuminating the state of the art subsequent to the priority date is not relevant to written description").

b. The Office Erred In Failing To Evaluate the Asserted Priority Date of Claim 21.

The Examiner did not consider Mizumura, the '498 PCT, or McClymont as prior art because the Examiner failed to consider written description and/or enablement in analyzing the facial priority claim of the '386 Application to

determine whether claim 21 was entitled to the December 10, 2012 priority date. With respect to claim 21, as discussed in Section IX, *infra*, this was material error, and under *Advanced Bionics*, step 2 does not support discretionary denial. *Nrg Energy, Inc. v. Midwest Energy Emissions Corp.*, No. IPR2020-00832, 2020 WL 6277239, at *6-7 (PTAB Oct. 26, 2020) (declining to deny institution under § 325 where the Examiner failed to consider during prosecution whether priority applications provided written description support for claims); *The Gillette Co. LLC v. Sphere USA, LLC*, PGR2022-00030, Paper 8, 40-41 (PTAB Sept. 23, 2022).

B. 35 U.S.C. § 314(a)

Because there is no ongoing litigation and there has been no challenge to the '318 patent to date, discretionary denial under § 314(a) would be inappropriate.

VII. LEVEL OF ORDINARY SKILL IN THE ART

A POSA in the technical field relating to the '318 patent would have a Ph.D. degree in biological, chemical or biochemical engineering, molecular biology, or biochemistry and at least two years of experience utilizing or assessing horseshoe crab Factor C (lysate, purified native and/or recombinantly produced) for endotoxin detection and quantitation. More education could substitute for experience, and vice versa. Jain, ¶¶61-66.

VIII. CLAIM INTERPRETATION

Claim terms subject to *inter partes* review are to be “construed...in accordance with the ordinary and customary meaning of such claim as understood

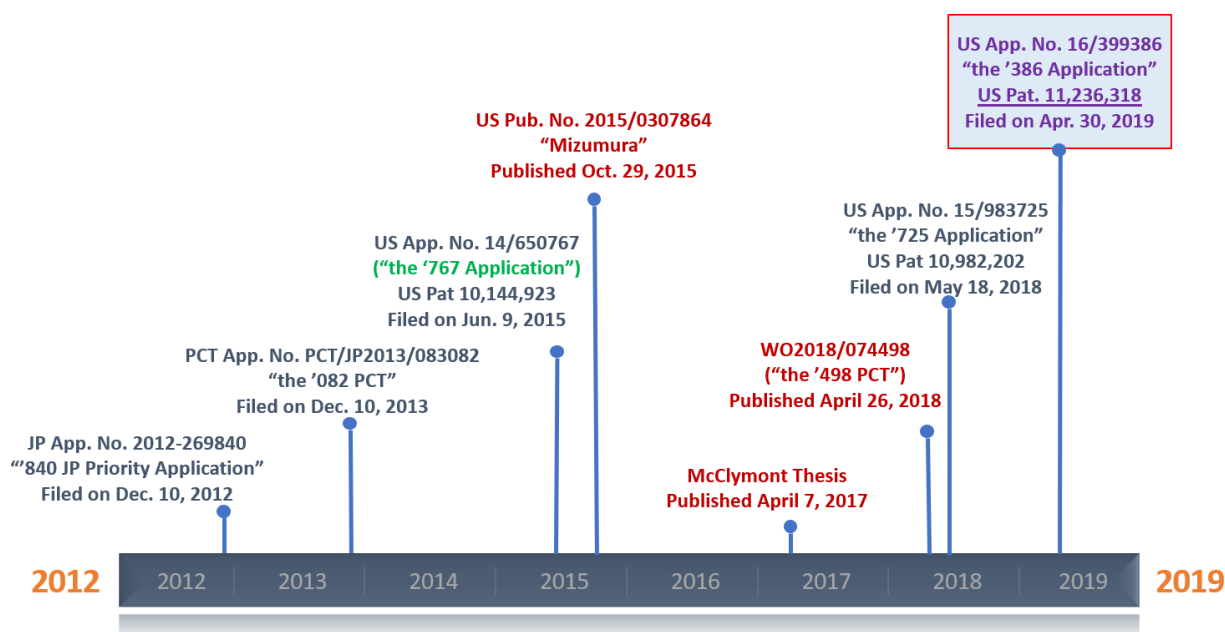
by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.200(b). Because the Petition’s prior art plainly render the claims unpatentable under any plausible construction, no outer boundary constructions are necessary. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017).⁴ Jain, ¶71.

IX. CLAIM 21 IS ENTITLED TO AN EFFECTIVE FILING DATE NO EARLIER THAN THE ’318 PATENT’S ACTUAL FILING DATE.

A. The ’318 Patent’s Priority Claim

As shown in the timeline and discussed below, the ’318 patent claims priority through a series of near-identical continuation applications to a Japanese Priority Application (2012-269840) (“the ’840 JP Priority Application”) (EX1019) filed Dec. 12, 2012.

⁴ *See generally Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005); 37 C.F.R. § 42.200(b). Nothing in this IPR is a concession as to the scope of any claim term in litigation, or a waiver of any indefiniteness argument.



The '840 JP Priority Application is incorporated by reference into each application in the '318 patent priority chain. It discloses less than the '082 PCT and later-filed utility applications (for example, it includes the experiments and results numbered (1)-(5), including Figure 7, but not experiments (6)-(10)). Compare EX1019, ¶¶0096-134 *with* EX1035. While the '840 JP Priority Application discloses residual activity in the presence of sodium citrate using “greater than 10%” (as opposed to “10% or greater” as later claimed), it provides no residual activity range for magnesium sulfate at all. EX1019, ¶¶0018; Jain, ¶¶72-73.

Upon U.S. entry of the '082 PCT on June 9, 2015, Patent Owner amended the specification to add a paragraph relating to the zymogen cascade reaction. EX1020, 2-3. This paragraph appears in the subsequent '725 and '386

Applications, and in the '318 patent specification, which are otherwise identical to the '082 PCT and '767 Application. EX1001, 13:8-21; Jain, ¶¶74.

For purposes of analyzing entitlement to the claimed priority date of December 10, 2013, this Petition analyzes and cites to the '767 Application (including the added paragraph, EX1020) as representative of each disclosure (including the '840 JP Priority Application and the '082 PCT (Ex. 1035)) in the priority chain extending back to December 10, 2012. If the representative '767 Application fails to describe and enable claim 21, the '840 JP Priority Application and all other applications in the priority chain fail for the same reasons (including the June 9, 2015 filing date of the '767 Application itself). Jain, ¶¶46-47, 75.

B. The '767 Application Lacks Written Description Support for the Recombinant *Limulus Polyphemus* Factor C Proteins Having Residual Activity Across the Full Scope of the Claimed Range.

For claim 21 to benefit from a December 10, 2013 filing date, “each application in the chain leading back to the earlier application must comply with” the requirements of 35 U.S.C. § 112. *Arthrex, Inc. v. Smith & Nephew, Inc.*, 35 F.4th 1328, 1343 (Fed. Cir. 2022) (affirming Board’s determination that challenged claims were not entitled to earlier priority date).

The representative '767 Application lacks written description support for issued claim 21 as required by 35 U.S.C § 112 and governing case law, as it does not demonstrate to a POSA that the inventors possessed the full scope of that claim

as of December 10, 2013. April 30, 2019 (the actual filing date of the '318 patent) is therefore the effective filing date of that patent. 35 U.S.C. § 100(i)(1). Jain, ¶76.

1. The Inventors Did Not Possess *Limulus Polyphemus* Factor C Proteins With Claim 21's Functional Requirements as of 2013.

Claim 21 requires that the *Limulus polyphemus* Factor C protein “exhibits a residual activity of at least one selected from the group consisting of:

(1) 10% or higher in the presence of 21 mM sodium citrate; and

(2) 15% or higher in the presence of 16 mM magnesium sulfate.” EX1001,

cl. 21. This claim encompasses a genus of recombinantly produced *Limulus polyphemus* Factor C proteins satisfying either one of these exceedingly wide ranges for the functional characteristic of “residual activity.” *Id.*; Jain, ¶¶45, 77-78.

The '767 Application purports to disclose experimental protocols for making—and data demonstrating that recombinant Factor C of the *Tachypleus tridentatus species*, when produced in HEK293 cells, yields—Factor C proteins with a “residual activity” falling within the claimed range. EX1006, 83-99. For sodium citrate, the '767 Application describes only a HEK-produced *Tachypleus tridentatus* recombinant Factor C protein with a residual activity of approximately 25. EX1006, 96-99, 122 (FIG. 7). It describes no other example of such a protein with a residual activity of any other value within the wide range of “10% or higher.” For magnesium sulfate, the '767 Application describes only a HEK-

produced *Tachypleus tridentatus* recombinant Factor C protein with a residual activity of 23. *Id.* It describes no other example of such a protein with a residual activity of any other value within the range of “15% or higher.” Jain, ¶¶79-81.

A POSA would not expect such protocols to yield recombinant proteins in soluble and functional form from a **different** species of crab (whose full sequence information was not even known as of 2013) let alone expect that such unknown and uncharacterized proteins would exhibit a function—residual activity—falling in and across the full scope of the claimed range without completing the invention by sequencing the claimed proteins and engaging extensive testing to assess function or by elucidating a verified structural explanation for such function across species. Jain, ¶¶82-84. *See In re Alonso*, 545 F.3d 1015, 1020 (Fed. Cir. 2008) (affirming lack of written description—“[I]t is **not enough** to describe[] the procedure for making a human-human hybridoma from neurofibrosarcoma, and teach how to determine whether a given antibody, specific to a patient’s neurofibrosarcoma, will function in the claimed method.”); *Gevo, Inc. v. Butamax Advanced Biofuels LLC*, 13–576–SLR, 2013 WL 3914467, *15 (D. Del. July 26, 2013) (for claims to recombinant yeast microorganism producing yield of at least 10%, granting summary judgment of invalidity for lack of written description where specification only described yields of about 13% and provided no detail on how to practice claim to achieve higher yields in range).

And while the *Limulus polyphemus* Factor C sequence information was elucidated and disclosed in 2017, years **after** the claimed priority date of the '318 patent, such “later-acquired knowledge” of a gene is not relevant to possession as of claimed priority date. *Billups-Rothenberg*, 642 F.3d at 1037. Jain, ¶85.

a. The '767 Application Does Not Mention or Describe a Single Example of the Claimed Recombinant *Limulus polyphemus* Factor C Proteins, Let Alone One Satisfying the Claimed Function.

The '767 Application does not disclose **any** example (prophetic or experimental) of **any** recombinant protein from *Limulus polyphemus* (*i.e.*, the American horseshoe crab), let alone any such protein with claim 21's functional requirement. Instead, it focuses entirely on a different and geographically segregated species of crabs—*Tachypleus tridentatus* (*i.e.*, the Japanese horseshoe crab). Even *Carcinoscorpius rotundicauda* (*i.e.*, the Singaporean horseshoe crab) is mentioned only for molecular weight comparison. Every experimental example, table entry, and gene and amino acid sequence listing in the '767 Application concerns the Japanese and Singaporean species. Jain, ¶¶67-68, 86.

Without the ability to make or describe the function of any recombinant Factor C protein from the claimed *Limulus polyphemus* species of horseshoe crab—whose gene and amino acid sequence was not yet known or disclosed by 2013—the inventors did not and could not describe **a single example** of a *Limulus polyphemus* Factor C protein recombinantly produced via HEK293 cells (or by any

other mammalian cell) that falls within the claimed range of residual activity in the presence of the recited ions, let alone across its full scope. Jain, ¶¶69-70, 87. The absence of working examples and other information from which a POSA would have understood the inventor to have possessed the claimed functional material supports a finding of no written description. *Boston Sci. Corp. v. Johnson & Johnson Inc.*, 647 F.3d 1353, 1364 (Fed. Cir. 2011) (for claims directed to macrocyclic lactone analogs of rapamycin, affirming no written description where, “[t]he shared specification lists ‘Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones)...[but] four experimental delivery methods using only rapamycin are detailed. No experiments are detailed using macrocyclic lactone analogs nor does the specification even indicate performance of any such experiments....[The shared specification] does not evidence possession of the genus of macrocyclic lactone analogs of rapamycin in the claimed invention to inhibit restenosis.’”).

Where geography separated these species of crabs (belonging to distinct taxonomic families Limulidae and Tachypleinae), giving rise to genetic and morphological distinctness, and where existing and limited sequence data for the *Limulus polyphemus* crab showed **differences** between its Factor C amino acid sequence and those of other species (discussed *infra*), the failure to provide any experimental example or verified structural link between species giving rise to

such similar function only confirms a lack of possession. Jain, ¶88; EX1038, 6-7, 10-15 (discussing the geographic and genetic discreteness of Family Limulidae and Family Tachypleinae); EX1022, 157.

b. Differences In Species and Known Differences in Sequence Would Be Expected To Yield Differences in Protein Function.

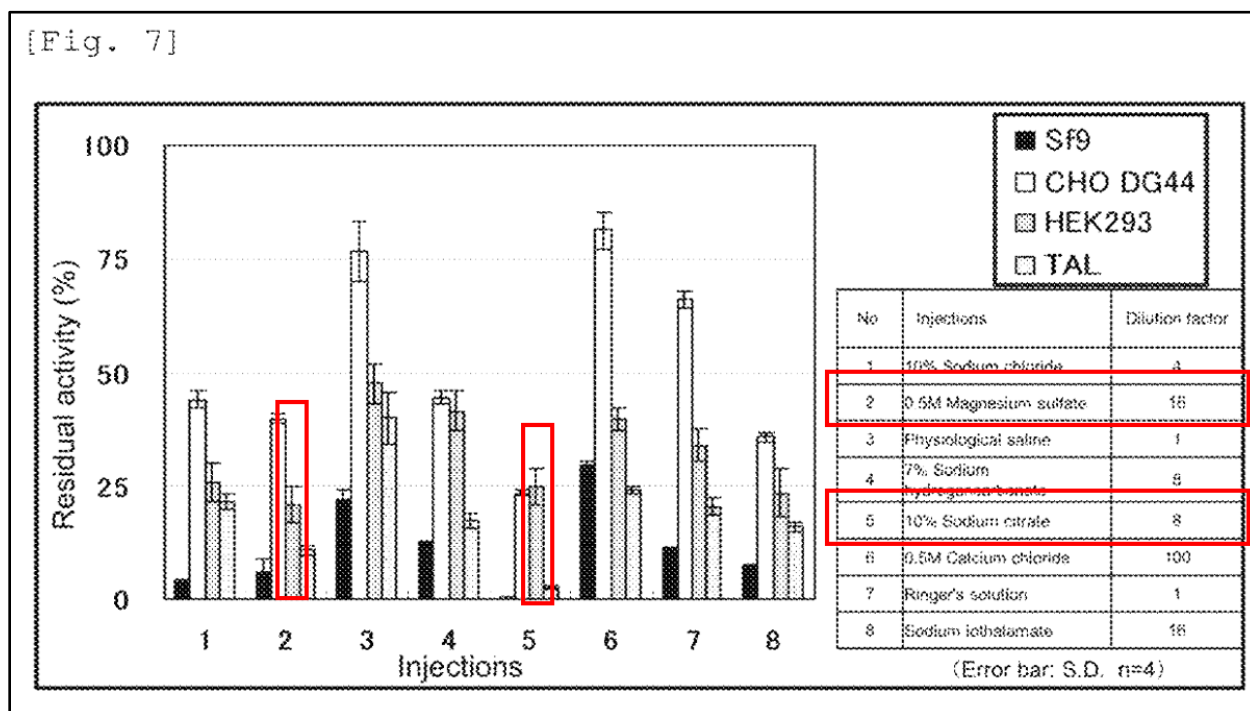
As of 2013, a POSA would have expected that differences in gene or amino acid sequence (as would be expected across different horseshoe crab species) lead to differences in protein structure, and, in turn, differences in protein function. As a result, using sequence homology (or, presumed similarity where a sequence is not yet characterized) to assume the existence of functional identity is an oversimplified understanding of protein function and subject to error. Jain, ¶89. POSAs at the time would have been familiar with the cautionary concept that “function similarity generally increases with sequence similarity but with a high degree of variability.” *Id.*, ¶¶90-92; EX1021, 1; EX1008, 2781. Without the full gene and amino acid sequence information for *Limulus polyphemus* Factor C in 2013 from which **any comparison** could even be made to any other species, any view about the resulting functional characteristics (specifically, across a wide range of residual activity) of a recombinantly produced protein from *Limulus polyphemus* would have been mere speculation. Jain, ¶93; *see also*, EX1010, 31-35.

The '767 Application itself references “conservative variation” as differences in amino acid sequences between species “where [] function of the protein is appropriately maintained.” EX1006, 47. However, as of 2013, a POSA would have known from very limited sequencing information about *Limulus polyphemus* Factor C proteins, that certain sequence differences between that species and *Tachypleus tridentatus* were **non-conservative** (i.e., potentially giving rise to changes in function in terms of enzymatic activity of Factor C). Jain, ¶¶94; EX1022, 157. Thus, by December 2013, and based on a partial amino acid sequence for *Limulus polyphemus* Factor C (compared with sequence information for *Tachypleus tridentatus* Factor C), it would have been apparent to POSAs that non-conservative mutations (including, for example, difference in a carbohydrate attachment site) between these species of horseshoe crabs exist, and they had a potential to cause structure and function differences between the recombinantly produced Factor C proteins. *Id.*, ¶¶95-101; EX1022, 157.

A POSA in 2013 would have understood that knowledge of a protein sequence giving rise to a particular function for one species (i.e., *Tachypleus tridentatus*) did not equate to possession of a protein sequence with a comparable function from a different, uncharacterized, species (i.e., *Limulus polyphemus*), let alone possession of such protein across an exceedingly wide range of residual activity function. Jain, ¶¶102-104.

c. The Inventors Failed To Provide A Structural Feature Common to the Claimed Genus That Correlates with Function From Which A Reasonable Expectation of Functional Comparability Could be Made.

Claim 21 encompasses a genus of HEK-expressed recombinant *Limulus polyphemus* Factor C protein whose residual activity is *either* 10% or higher in the presence of 21 mM sodium citrate *or* 15% or higher in the presence of 16 mM magnesium sulfate. The '840 JP Priority Application lacks any mention of any residual activity range or percent in the presence of magnesium sulfate whatsoever and so fails to support claim 21. *See generally*, EX1019. In addition, the '767 Application provides only a *single* measurement of HEK-expressed recombinant Factor C proteins in each ionic solution.



See EX1006, 122 (FIG. 7) (annotated). Even these two examples, however, were obtained via production of recombinant Factor C protein from *Tachypleus tridentatus* horseshoe crabs, and **not** *Limulus polyphemus* horseshoe crabs. Jain, ¶¶105-106.

The '767 Application provides no other explanation or structural feature common to such proteins that would indicate to a POSA that the inventors were in possession of the full scope of proteins with residual activities falling above the claimed thresholds for a different species of horseshoe crab. Though the '767 Application speculates that the addition of post-translation (α -2,3)-linked terminal sialic acid via expression in mammalian systems (such as HEK293 cells) could contribute to such increase in residual activity, Patent Owner and the inventors explicitly abandoned this theory for *Limulus polyphemus* proteins expressed in HEK293 cells in securing issuance of claim 21. EX1004, 77 (“[S]uperior salt tolerance can be reproduced irrespective of presence of (α -2,3)-linked terminal sialic acid, at least for *Limulus* Factor C recombinantly produced using HEK 293 cell as a host.”), 86 (same). Jain, ¶107.

Because the '767 Application does not disclose a single example of Factor C proteins satisfying either of the broad “residual activity” thresholds of claim 21, and because it also fails to disclose “structural features common to the members of the genus so that [a POSA] can ‘visualize or recognize’ the members of the

[functionally defined] genus,” the ’767 Application fails to satisfy the written description requirement. *See Boston Sci.*, 647 F.3d at 1363 (for claims directed to a large genus of stents using macrocyclic lactone analogs, affirming summary judgment of no written description where the specification failed to show a correlation between the structure of the claimed analog and the function it was described and claimed to perform). Instead, the inventors of the ’767 Application left it to others to elucidate the gene an amino acid sequence for *Limulus polyphemus* Factor C protein, figure out how to recombinantly express such protein in functional form, and figure out how to recombinantly express such protein in a manner that its residual activity satisfies the specific threshold of claim 21, across the full claimed range. This research plan fails to amount to written description support. *See Carnegie Mellon Univ. v. Hoffmann-La Roche, Inc.*, 541 F.3d 1115, 1126 (Fed. Cir. 2008); *Butamax*, 2013 WL 3914467, *15; Jain, ¶¶108-110.

2. The ’318 Patent Inventors Admitted that the Invention of Recombinant *Limulus polyphemus* Factor C Was Not Completed Until Years After the Claimed Priority Date.

That the inventors did not possess recombinant *Limulus polyphemus* Factor C proteins having the claimed functional property is confirmed by their own admissions to the patent office. On October 18, 2017, two of the three inventors named on the ’318 patent (Mizumura and Oda) filed WO 2018/074498 (“the ’498

PCT”) (EX1005). In this PCT, the inventors detailed the struggle the field encountered in accomplishing the recombinant production of *Limulus polyphemus* proteins—“[t]here have been no reports of a reagent using recombinant proteins derived from *Limulus polyphemus*, which is widely used as a lysate reagent.” EX1005, ¶¶0007-09. The ’498 PCT explains that “[t]he reason is that in *Limulus polyphemus*, the proteins and their genes involved in the mechanism of coagulation caused by endotoxin **have not been completely identified structurally or functionally.**” *Id.*, ¶0010. This admitted absence of any known link between structure and function is fatal to the question of written description support for claim 21. *Boston Sci.*, 647 F.3d at 1366-67 (no written description support where the “shared specification indicates that the alleged correlation between structure and function was ***not well known*** by the effective filing date”); Jain, ¶¶111-112.

Instead, as in *Boston Scientific Corp. v. Johnson & Johnson*, the ’498 PCT inventors explained that a predictable correlation between structure and function of *Limulus polyphemus* Factor C proteins was not well known by the priority date of the ’318 patent and explicitly attribute this unpredictability to biodiversity. EX1005, ¶¶0012-13 (“[D]ue to the various differences and diversity of biomolecules depending on the genus and species of horseshoe crab, it has not been possible to accurately determine the full-length sequence structure,

expression, and function of these proteins and genes using conventional methods.”). Jain, ¶113.

In the ’498 PCT, however, inventors Mizumura and Oda tout their own more **recent**—and by their own admission, non-trivial—success: “in obtaining full-length cDNAs encoding all of the protein factors involved in the coagulation mechanism of *Limulus polyphemus*, something that no one had succeeded in doing for many years...thereby completing the present invention.” *Id.*, ¶0017. These inventors indisputedly did not possess (by 2013) the invention of claim 21—a recombinant protein from *Limulus polyphemus* defining boundaries **excluding** every example (related to the entirely separate *Tachypleus* species) that the ’767 Application discloses. Jain, ¶114; see *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1562-63, 1567 (Fed. Cir. 1997) (for claims to recombinant organism expressing human cDNA, affirming invalidity for lack of written description where specification only disclosed rat cDNA, provided no structural or functional link between rat and human cDNA, and inventors did not clone the human cDNA **until two years after** disputed application was filed).

As discussed in Section IX.B.1 *supra*, and per the inventors themselves, there were **known** amino acid sequence differences between *Limulus polyphemus* crabs and other species such that predictions about function would have been speculative. Jain, ¶115; EX1022, 157; EX1005, ¶0012. Such variation between

species demonstrates a lack of possession of functional proteins in the absence of sequence information. In *Carnegie Mellon University v. Hoffmann-La Roche, Inc.*, the Federal Circuit, citing *Regents v. Eli Lilly*, found that the failure to disclose nucleotide sequence information or other descriptive features for a *polA* gene—a critical aspect to the claimed recombinant plasmid invention—from any source other than *E. coli*, was fatal to the inventor’s attempt to demonstrate possession of a wider claimed genus of recombinant plasmids that contained coding sequences from any bacterial source. 541 F.3d at 1125-26 (affirming no written description— “[G]iven the record evidence that the *polA* gene varied among the numerous bacterial species, as well as the absence of any *polA* gene sequence for any bacteria other than *E. coli*, we conclude that [the written description] requirement was not met here.”).

The ’318 patent inventors did not possess the claimed recombinant *Limulus polyphemus* Factor C protein in 2013—a fact they freely admitted when they later—having acquired the gene and amino acid sequence information for this species of crab—attempted to patent this very invention. At best, the ’767 Application invites a POSA to *try* to: (1) sequence the *Limulus polyphemus* Factor C gene despite the prior difficulty of doing so, (2) recombinantly produce this Factor C protein of claim 21 using the new information they discovered, and (3) do so across a wide claimed functional range, or unearth a structural feature driving

the protein's function as claimed. Jain, ¶¶116. Even if obvious to *try*, is well-settled that the obviousness of trying a particular course in view of a patent disclosure does not constitute adequate written description. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (no written description: "The question is not whether a claimed invention is an obvious variant of that which is disclosed," rather the "application itself must describe an invention, and do so in sufficient detail that [a POSA] can clearly conclude that the inventor invented the claimed invention."); *see also In re Kuenzel*, Appeal 2009-015373, 2011 WL 938717, at *5 (B.P.A.I. Mar. 17, 2011) (same); *Ariad*, 598 F.3d at 1352 (same).

C. The '767 Application Fails to Enable the Full Scope of Factor C Proteins Across the Claimed Range of Residual Activity Values.

Section 112(a) contains an enablement requirement separate from the written description requirement. *Ariad*, 598 F.3d at 1344. To satisfy the enablement requirement, "the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). "Claims are not enabled when, at the effective filing date of the patent, [a POSA] could not practice their full scope without undue experimentation." *Wyeth & Cordis Corp. v. Abbott Lab 'ys*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). "It is the specification, not the knowledge of [a POSA], that must

supply the novel aspects of an invention in order to constitute adequate enablement.” *Genentech*, 108 F.3d at 1366.

Undue experimentation factors include “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Claim 21 sweeps in recombinant Factor C proteins with residual activity values falling anywhere above very low thresholds (10% and 15%) when in the presence of defined concentrations of two ions—sodium citrate and magnesium sulfate, respectively. The ’767 Application describes only a single measurement in each ionic solution of recombinant Factor C for an *unclaimed* species of crab and zero examples or measurements of a recombinant protein for the claimed *Limulus polyphemus* horseshoe crab. And the ’767 Application merely reports on such result when the proteins are expressed via insect or mammalian expression systems, rather than explain *why* such values were obtained in each case relative to the claimed proteins. Again, while the inventors had surmised that such residual activity values were due to the post-translational addition of (α -2,3) sialic acid when such proteins were expressed in mammalian cells, they dropped this theory

to secure claim 21, telling the Patent Office that such theory did not apply to *Limulus polyphemus* recombinant proteins. EX1004, 77, 86; Jain, ¶¶117-121.

Accordingly, the '767 Application does not teach a POSA how to make or use recombinant *Limulus polyphemus* Factor C proteins with any particular residual activity value (whether that be inside or outside the claimed range, or at a value slightly higher than the threshold, or a value approaching 90 or 100). To do so a POSA would have needed to engage in significant experimentation to make proteins exhibiting a residual activity across such a wide claimed range. Jain, ¶¶122-128. Such would have amounted to a trial and error “research assignment[]” requiring an unreasonable amount of experimentation in violation of the enablement requirement of 35 U.S.C. § 112. *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023).

1. Wands Factor Analysis

a. Claim 21 is Broad (Factor 8).

Claim 21 broadly encompasses Factor C proteins satisfying a wide range of values of residual activity in the presence of certain ions. While the inventors abandoned the one structural characteristic offered in the '767 Application to potentially explain the purported functional advantage of the claimed invention—and eliminated this characteristic from claim 21—they provided no additional disclosure to enable a POSA to make and use the full scope of resulting proteins in

a manner amounting to anything more than a trial-and-error research assignment to “see what works.” *Amgen*, 598 U.S. at 613-14. Jain, ¶¶130-134.

Reaching the full scope of claim 21 therefore requires an extensive amount of experimentation across multiple fronts: (1) to discover and characterize the gene and amino acid sequence for *Limulus polyphemus* Factor C itself, which was not known as of 2013 (*see* Section IX.B, *supra*), (2) to use this as-yet undiscovered genetic information to recombinantly generate Factor C protein across the full scope of residual activity function characteristic as defined by claim 21. Jain, ¶135.

b. The Nature of the Invention, Lack of Information in the Prior Art, and Unpredictability of the Field Contributes to Unpredictability About The Residual Activity Across the Wide Range Claimed (Factors 4, 5, 7).

As discussed above, per the ’318 patent inventors’ own admission years after the ’767 Application was filed, the field had struggled to sequence *Limulus polyphemus* Factor C protein and could not make accurate predictions as to its structural and functional properties in view of the biodiversity between horseshoe crab species. EX1005, ¶¶0012-17; EX1038, 6-7, 10-15. Jain, ¶136.

In addition, while recombinant technology was not new as of 2013, a significant amount of research and experimentation was required to generate a particular protein, with a particular functional capability, across a number of different expression systems. The ’767 Application provides no guidance,

whatsoever, on how to control for residual activity—how to drive it higher or lower in HEK293 recombinant systems—and certainly provides no guidance on this in the *Limulus polyphemus* species of crab, specifically. A POSA would not have been able to predict or expect a particular level of “residual activity” from a *Limulus polyphemus* Factor C protein recombinantly produced as of 2013. Jain, ¶¶137-138.

c. The Level of Ordinary Skill in the Art Is High (Factor 6).

The level of ordinary skill in the art in the field of this purported invention is high. *See* Section VII, *supra*; Jain, ¶65. However, designing, expressing, and testing recombinant proteins is laborious, time-consuming, complicated, and highly unpredictable due to the many effects that variations in amino acid sequence (and subsequent post-translational modifications) can have on protein structure and function. *See* Section IX.B.1, *supra*. Additionally, making a recombinant Factor C protein that actually has ***any*** desired activity (i.e., ability to detect endotoxin) was known to be difficult in view of challenges, for example, with getting such proteins to be secreted by the host cells themselves. EX1026, 360; EX1027, 71. In view of this, making a recombinant Factor C protein with endotoxin detection function ***at or above a particular level*** was highly speculative. Jain, ¶¶139-140.

Thus, reaching the full scope of claim 21 would require a high level of skill. While the level of skill typically required to practice in this field is already high,

because of the lack of guidance in the '767 Application itself and elsewhere in the prior art, as discussed in at least Section IX.B above, such highly skilled individuals may *attempt* to practice the claimed invention but *still* be left with nothing but a “research assignment[]” to generate *Limulus polyphemus* Factor C proteins and to identify and explain how such proteins achieve a residual activity falling in the claimed range. Jain., ¶141; *Amgen*, 598 U.S. at 614.

d. The Absence of Guidance or Examples in the '767 Application Necessitates Undue Experimentation to Practice the Full Scope of Claim 21 (Factors 1-3).

While claim 21 includes *Limulus polyphemus* recombinant proteins across a wide range of “residual activity” levels, the '767 Application never describes or instructs a POSA how to make or use *any* recombinant proteins from this species of crab at all. The '767 Application provides no working examples of such proteins. And nothing in the application suggests any steps the inventors envisioned for ensuring that such *Limulus polyphemus* Factor C proteins (when they were eventually made) would satisfy the claimed residual activity requirement. Even assuming the '318 patent inventors had a plan for generating these *Limulus polyphemus* proteins, they provided no guidance whatsoever on how to execute that plan. Jain, ¶¶142-43. *See Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999) (claims to an antisensing DNA technique applied to prokaryotic and eukaryotic cells were invalid for lack of enablement where the

specification disclosed application of the technique only to genes relating to prokaryotic cells and there was no disclosure of how to practice the technique with eukaryotic cells—“[T]he teachings set forth in the specifications provide no more than a ‘plan’ or ‘invitation’ for [a POSA] to experiment practicing antisense in eukaryotic cells; they do not provide sufficient guidance or specificity as to how to execute that plan.”).

As of 2013, the generation of recombinant Factor C proteins from a different species of crab and across a wide range of functional capabilities would have required literature review, the obtaining of sequences, the preparation of precursors, optimization of the experimental conditions, the obtaining and purifying of Factor C with various levels of sialic acid, and the verification of residual activity at lower, moderate, and higher values with then-claimed “10% or higher” and “15% or higher” thresholds. However, the ’767 Application makes no mention of what logic or protocol a POSA would use to generate recombinant Factor C proteins with the functional characteristics across the full scope of the alleged claimed invention (e.g., 90% or 95%). In the absence of any such disclosure, the ’767 Application fails to enable the full scope of claim 21. Jain, ¶¶144-46. *See MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1381-84 (Fed. Cir. 2012) (affirming judgment that claims directed to an electrical memory device that could have “a change in the resistance by at least 10%” were

invalid where the specification only enabled changes in resistance up to about 12%—“The open claim language chosen by the inventors does not grant them any forgiveness on the scope of required enablement....The ’922 patent specification only enables [a POSA] to achieve a small subset of the claimed range. The record contains no showing that the knowledge of that artisan would permit, at the time of filing, achievement of [higher values] without undue experimentation.”); *Medytox*, 71 F.4th at 998-99.

The ’767 Application neither describes nor enables the full scope of claim 21, which is entitled to an effective filing date of no earlier than April 30, 2019.

X. THE PRIOR ART

A. Mizumura (EX1009)

U.S. Patent Publication No. 2015/0307864 (“Mizumura”) is the October 29, 2015 publication of the ’767 Application. Excepting the paragraph added with the filing of the ’767 Application (EX1020, 2-3), Mizumura has an identical disclosure to the ’318 patent (*compare* EX1009, *with* EX1001). Jain, ¶¶147-150.

If challenged claim 21 is entitled to an effective filing date of no earlier than April 30, 2019, then Mizumura is prior art to claim 21 under post-AIA 35 U.S.C. § 102(a)(1). None of the exceptions in 35 U.S.C. §102(b)(1) apply, as the ’498 PCT was published more than one year prior to the April 30, 2019 effective filing date of claim 21. *See Indivior UK Ltd. v. Dr. Reddy’s Lab’ys S.A.*, 18 F.4th 1323, 1329-

30 (Fed. Cir. 2021). Claim 21 is subject to the first-to-file provision of the AIA because, if the '318 patent is not entitled to an effective filing date of December 10, 2012, then the effective filing date falls after March 16, 2013. *See* AIA, Pub. L. 112-29, 125 Stat. 284, § 3(n)(1) (2011). The next application in the '318 patent's priority chain was filed on December 10, 2013.

In addition, as noted above, in view of a Transition Application Certification filed during prosecution of the '725 Application (EX1011), all subsequent prosecution of applications in the continuity chain of the '318 patent were treated as subject to post-AIA law.

B. The '498 PCT (EX1005)

The '498 PCT was filed on October 18, 2017 and published on April 26, 2018. If claim 21 of the '318 patent is not entitled to an effective filing date earlier than April 30, 2019, then the '498 PCT is prior art to claim 21 under post-AIA 35 U.S.C. §102(a)(1). None of the exceptions in 35 U.S.C. §102(b)(1) apply, as the '498 PCT was published more than one year prior to the April 30, 2019 effective filing date of claim 21.

The '498 PCT is the publication of an unrelated patent application filed by Patent Owner, sharing two common inventors (Mizumura and Oda) with the '318 patent. EX1005, front (72). The “present invention” of the '498 PCT “relates to

recombinant proteins derived from the genus *Limulus*, DNA encoding the same, and methods of use thereof.” *Id.*, ¶¶0001; Jain, ¶¶151-52.

C. McClymont 2017 (EX1010)

McClymont is a University of Glasgow Ph.D. Thesis by Karen McClymont, dated March, 2017, and deposited for public accessibility on April 7, 2017. If claim 21 of the ’318 patent is not entitled to an effective filing date of earlier than April 30, 2019, then McClymont is prior art to claim 21 under post-AIA 35 U.S.C. §102(a)(1). None of the exceptions of 35 U.S.C. §102(b)(1) apply, as McClymont was published more than one year prior to the April 30, 2019 effective filing date of claim 21. Jain, ¶153.

McClymont discusses the need for complete sequence information for Factor C from *Limulus polyphemeus* horseshoe crabs given intra-species variability in binding site structure. EX1010, 36 (“Despite the fact that other Factor C based tests use protein from the *Tachypleus tridentatus* and *Carcinoscorpius rotundicauda* species, the commercial LAL [(Limulus amoebocyte lysate)] test is made from *Limulus* Factor C. ***As there are known variances between different LPS binding sites, it is beneficial to study lpFC to identify any differences that may arise between the species in terms of sensitivity or specificity of binding.***”), 38.

McClymont reported that “[n]either the amino acid, nor the genomic DNA or cDNA sequences for Factor C from *Limulus polyphemus* were available in any

public databases” and described the research and results of her endeavor “to assemble the *Limulus polyphemus* Factor C coding sequence and gene” in 2017. *Id.*, 38-39, 159-60. McClymont was publicly available and publicly accessible at the University of Glasgow as of its date of deposit of April 7, 2017. EX1010, 1. Jain, ¶¶154-155.

XI. PRECISE REASONS FOR RELIEF REQUESTED

A. Ground 1: Claim 21 Is Obvious Over Mizumura In View of The '498 PCT.

Mizumura’s disclosure is identical to both the ’767 Application and the ’318 patent specification⁵ and it discloses recombinantly produced Factor C having the residual activity properties of challenged claim 21. EX1009, ¶¶0035, 0099, 0179, 0203, 0311, FIG. 7; Jain, ¶156.

The ’498 PCT is an international publication disclosing the production of *Limulus polyphemus* recombinant Factor C via mammalian recombinant expression systems. EX1005, ¶¶0037-39, 0155-185; Jain, ¶157.

In view of the movement in the field of Factor C protein use for endotoxin testing toward the generation of recombinant Factor C proteins as a substitute for

⁵ Excepting the paragraph that was added with the U.S. conversion of the ’082 PCT to the filing of the ’767 Application. EX1020. This paragraph does not impact the determination of obviousness. Jain, ¶¶64, 156.

harvesting blood from native crabs (EX1005, ¶¶0007-09), by April of 2019 POSAs would have had reason to modify Mizumura with the teachings of the '498 PCT to produce recombinant *Limulus polyphemus* Factor C proteins and would have had a reasonable expectation of success that such proteins would exhibit the residual activity of claim 21. Jain, ¶¶158-160. No evidence of secondary considerations rebuts this case of obviousness.

1. Legal Standard for Obviousness

The Board can (and should) conclude that Mizumura in view of the '498 PCT renders obvious claim 21, even though the same disclosure from Mizumura (in the form of the '767 Application) fails to provide written description support for that claim as a priority document. For purposes of the written description requirement in a priority analysis, “[i]t is the *disclosures of the applications* that count. Entitlement to a filing date does not extend to subject matter which is not disclosed but would be obvious over what is expressly disclosed.” *Lockwood*, 107 F.3d at 1571-72; *Ariad*, 598 F.3d at 1352.

While the disclosure of Mizumura is insufficient to demonstrate that the inventors had possession of the full scope of the functionally-claimed recombinant *Limulus polyphemus* Factor C proteins recited in claim 21 as of December 10, 2013 (*see* Section IX.B, *supra*), the teachings provided in Mizumura (of Factor C from the *Tachypleus tridentatus* species recombinantly produced via HEK293 cells

to have the claimed “residual activity”) when modified based on the teachings of the ’498 PCT (describing the sequence information for and successful recombinant production of functional *Limulus polyphemus* Factor C proteins) renders claim 21 obvious as of 2019. *See Parus Holdings, Inc. v. Google LLC*, 70 F.4th 1365, 1374 (Fed. Cir. 2023) (precedential) (affirming PTAB’s conclusion that challenged claims did not meet written-description requirement and were thus not entitled to a priority date antedating intervening prior-art reference (identical publication of challenged patent) that rendered claims obvious).

Likewise, a finding of nonenablement (as discussed in Section IX.C, *supra*) is not inconsistent with a finding of obviousness as the two patentability inquiries focus on different standards. For enablement, the specification must enable the full scope of the claim, whereas the obviousness inquiry is satisfied if the prior art renders obvious at least one embodiment falling anywhere within the scope of the claim. *In re Mraz*, 455 F.2d 1069, 1072-73 (C.C.P.A. 1972) (“[C]laims are unpatentable when they are so broad as to read on obvious subject matter even though they likewise read on non-obvious subject matter.”). Thus, while the ’318 patent inventors did not enable the full scope of claim 21 because its scope broadly includes recombinantly produced Factor C across a wide range of residual activity levels with no commensurate disclosure in the ’767 Application, a finding to this effect is not inconsistent with the determination that it would have been obvious to

produce a *Limulus polyphemus* recombinantly-produced Factor C protein within claim 21's scope (i.e., an example falling within the claimed range). *Pharm. Res., Inc. v. Roxane Lab 'ys, Inc.*, No. 03-3357, 2006 WL 3231427, at *16 (D.N.J. Nov. 8, 2006) (expert testimony that full scope of asserted claims was not enabled because POSA is not taught how to practice the full scope of the claim was not inconsistent with opinion that it would have been obvious to arrive at invention through other chemical experimentation); *see also Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc.*, 777 F. Supp. 330, 373-74 (D. Del. 1991).

2. Mizumura and the '498 PCT Collectively Disclose Each and Every Limitation of Claim 21.

As shown below, Mizumura and the '498 PCT disclose recombinantly produced Factor C proteins with all the characteristics recited in claim 21. Jain, ¶161-162.

Claim Term	Mizumura (EX1009)	'498 PCT (EX1005)
[21PRE] A horseshoe crab Factor C protein having activity of Factor C,	<i>“The Factor C of the present invention is a Factor C derived from a horseshoe crab.</i> The Factor C of the present invention is a recombinant protein. 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. <i>The Factor C of the present invention has activity of Factor C.</i> EX1009, ¶0187.	“Recombinant proteins derived from genus <i>Limulus</i> , and DNA molecules encoding same.” EX1005, Title. “The present invention relates to recombinant proteins derived from the genus <i>Limulus</i> , DNA encoding the same, and a methods of use thereof.” EX1005, ¶0001.

Claim Term	Mizumura (EX1009)	'498 PCT (EX1005)
		“An example of a protein having factor C activity is protein 1. <i>The first protein is specifically any of the following proteins:</i> <i>(I) A protein comprising the amino acid sequence of the protein having factor C activity of Limulus polyphemus.</i>” EX1005, ¶¶0082-83. “As a result, there was a success for the first time in expressing and obtaining a protein from <i>Limulus polyphemus</i> that may have factor C activity (sequence number 2), a protein that may have factor B activity (sequence number 6), and a protein that may have pro-clotting enzyme activity (sequence number 14).” EX1005, ¶¶0179-80.
[21A] wherein the horseshoe crab is <i>Limulus polyphemus</i> ,	“Meanwhile, it has been known that the American horseshoe crab (<i>Limulus polyphemus</i>) undergoes blood clotting when it is infected with a Gram-negative bacterium. This phenomenon has been conventionally employed for the detection of endotoxin.” EX1009, ¶¶0003, 0188.	“The present invention relates to recombinant proteins derived from the genus <i>Limulus</i>, DNA encoding the same, and methods of use thereof.” EX1005, ¶0001. “As a result, there was a success for the first time in expressing and obtaining a protein from <i>Limulus polyphemus</i> that may have

Claim Term	Mizumura (EX1009)	'498 PCT (EX1005)
		factor C activity (sequence number 2).” EX1005, ¶¶0179-80. “The genus <i>Limulus</i> contains only one species, <i>Limulus polyphemus</i>.” EX1005, ¶¶0004, 0017, 0155-0185 pp. 49-75. <i>See also</i>, EX1010, 46-48, 159-160.
[21B] and wherein the horseshoe crab Factor C protein is produced through being recombinantly expressed from a Human Embryonic Kidney (HEK) 293 cell, and	“The Factor C of the present invention may be produced through, for example, expression in a mammalian cell as a host....The mammalian cell is not particularly limited, so long as the cell can functionally express a horseshoe crab Factor C....The mammalian cell is preferably a cell of a mammal selected from the group consisting of a rodent and a primate.... Of these, human is preferred. Examples of the human cell include human embryo kidney (HEK) cell line. Examples of HEK include HEK293.” EX1009, ¶¶0205-06. “FIG. 6 A table and a graph showing the activity of the four types of Factor C (Sf9, CHO, HEK, and TAL) derived from Japanese horseshoe crab (<i>Tachypleus tridentatus</i>).” EX1009, ¶0178.	“Host cells other than horseshoe crab are not particularly limited, so long as they are capable of functionally expressing a protein from the first cDNA. Host cells other than those of horseshoe crab include, for example, mammalian cells and insect cells....Human cells include human embryonic kidney (HEK) derived cell lines. An example of HEK is HEK293.” EX1005, ¶¶0039, 155-185.

Claim Term	Mizumura (EX1009)	'498 PCT (EX1005)
	“FIG. 7 A table and a graph showing the activity inhibition by injections of the four types of Factor C (Sf9, CHO, HEK, and TAL) derived from Japanese horseshoe crab (<i>Tachypleus tridentatus</i>).” EX1009, ¶0179. <i>See also</i> EX1009, ¶¶0288-90.	
[21C] wherein the Factor C protein exhibits a residual activity of at least one selected from the group consisting of:	“The Factor C of the present invention may have low susceptibility to inhibition of activity by an ion....The ‘residual activity’ is defined as a relative reactivity (%) observed for a measurement specimen (endotoxin concentration: 0.05 EU/mL) prepared by adding endotoxin to an ion-containing test specimen, with respect to the reactivity observed for another measurement specimen (endotoxin concentration: 0.05 EU/mL) prepared by adding endotoxin to injection water as 100%, in the assay system shown in FIG. 4.” EX1009, ¶0203. “Activity of Factor C was measured through the procedure shown in FIG. 4. A residual activity was defined as a relative reactivity (%) for endotoxin in an injection specimen, with respect to the reactivity for endotoxin in the corresponding control specimen as 100%.” EX1009, ¶0311.	

Claim Term	Mizumura (EX1009)	'498 PCT (EX1005)
[21C1] (1) 10% or higher in the presence of 21 mM sodium citrate; and	“The above-described Factor C, which exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate.” EX1009, ¶0099. “FIG. 7 A table and a graph showing the activity inhibition by injections of the four types of Factor C (Sf9, CHO, HEK, and TAL) derived from Japanese horseshoe crab (<i>Tachypleus tridentatus</i>).” EX1009, ¶0179, FIG. 7 (showing bar graphs for No. 5 “Sodium citrate” as around 25% (for HEK293 cells)).	
[21C2] (2) 15% or higher in the presence of 16 mM magnesium sulfate.	“The above-described Factor C, which exhibits a residual activity of 15% or higher in the presence of 16 mM magnesium sulfate.” EX1009, ¶0035. “FIG. 7 A table and a graph showing the activity inhibition by injections of the four types of Factor C (Sf9, CHO, HEK, and TAL) derived from Japanese horseshoe crab (<i>Tachypleus tridentatus</i>).” EX1009, ¶0179, FIG. 7 (showing bar graphs for No. 2 “Magnesium sulfate” as around 20% (for HEK293 cells)).	

3. A POSA Would Have Had Reason to Modify Mizumura with the Teaching of the '498 PCT by April 30, 2019.

By April 30, 2019, POSAs not only had the full Factor C gene and amino acid sequence for *Limulus polyphemus* available, but as discussed below, they had reason to use such information to develop recombinant *Limulus polyphemus* Factor C via HEK293 cells with the “residual activity” described in Mizumura. Jain, ¶163.

a. *Limulus polyphemus* Factor C Was Known as the Critical Component of Existing and Widely-Used Endotoxin Assays.

Use of Factor C sourced from *Limulus polyphemus* horseshoe crabs in the LAL test dates back to the early 1960's. EX1023, 265. This advance—based on a natural characteristic of horseshoe crabs—is widely regarded as having critically improved safety and quality control in the biomedical industry. EX1024, 54-58 (“The discovery, commercialization, and use of LAL has been an important improvement to the pharmaceutical industry.”). By the first decades of the 21st century, the value of hemolymph from *Limulus polyphemus* horseshoe crabs, specifically, was clear. EX1016, 110, 116-117 (“*Limulus* test...has been widely employed as a simple and very sensitive assay method for bacterial endotoxins.”). Jain, ¶¶164-165.

The medical device and pharmaceutical industries have relied on the public trust and confidence in their products that was made possible by the LAL

endotoxin assay. EX1028, Abstract. Indeed, the inventors of Mizumura and the '498 PCT touted the value that native *Limulus polyphemus* Factor C had provided as a critical component of endotoxin detection since the early 1960's. *See generally*, EX1023; EX1009, ¶0003 (“[I]t has been known that the American horseshoe crab (*Limulus polyphemus*) undergoes blood clotting when it is infected with a Gram-negative bacterium. This phenomenon has been conventionally employed for the detection of endotoxin.”); EX1005, ¶0005 (“[A]moeboocyte lysates are widely used as a highly sensitive reagent for detecting endotoxin in the quality control of pharmaceuticals.”). Jain, ¶¶166-167.

b. Limitations of the LAL Assay Prompted Research for Alternative Endotoxin Detection Methods.

As important as the LAL assay has been to the biomedical industry, it is not without flaws; and “lack of specificity” of the test to particular endotoxins was a limitation prompting research into more specific alternatives. EX1025, 501 (“Problems with the specificity of LAL to endotoxin and the potential for negative effects on horseshoe crab populations have called for an alternative reliable endotoxin test.”), 507-8; EX1028, Abstract (“[V]ariations in sensitivity and specificity of LAL to endotoxin, and the limited supply of *limulus* (horseshoe crabs) has called for an alternative pyrogen test.”); EX1010, 26; Jain, ¶168.

Thus arose efforts to generate synthetic versions of the zymogen proteins (Factor B, Factor C, and Pro-clotting enzyme) involved in the clotting cascade of

horseshoe crabs. This included calls for utilizing increasingly popular recombinant technology to generate recombinantly-produced versions of Factor C (“rFC”) from particular species of crabs. EX1028, Abstract; *see also* EX1025, 507-508 (“The rapid and specific detection of endotoxin is urgently needed for the development and production of clinical drugs and medical devices where state-of-the-art pyrogen-free facilities are required.”). But, of course, in order to match or outperform the detection ability of the existing LAL test, such recombinantly produced *Limulus polyphemus* proteins had to demonstrate the functional ability to detect endotoxin. *Id.*; Jain, ¶¶169-170.

Given the biomedical research industry’s reliance on the ability to detect endotoxin in medical products so as to avoid associated adverse events, the desire to maximize endotoxin detection activity is and has been a core motivation in this field. EX1025, 507-8. POSAs would have had reason to maximize endotoxin detection—maximizing the claimed “residual activity” in the presence of inhibitory ions—in an effort to produce recombinant horseshoe crab proteins to replace those natively-sourced. Jain, ¶¶171-172.

As discussed above, knowledge about how to accomplish the recombinant production of Factor C from different species of horseshoe crab was acquired at different times. While prior to 2017, scientists had the “idea to artificially produce proteins in amebocyte lysate using recombinant technology” and while certain

companies had already commercialized products involving the recombinant proteins from the *Tachypleus* and *Carcinoscorpius* species of crabs, (EX1005, ¶0008), as the '498 PCT explains, the structural and functional characterization of the proteins involved in clotting from *Limulus polyphemus* horseshoe crabs remained elusive. *Id.*, ¶¶0008-13. But by 2017 this identification was accomplished. By the April 26, 2018 publication of the '498 PCT, those inventors described having “succeeded in obtaining full-length cDNAs encoding all of the protein factors involved in the coagulation mechanism of *Limulus polyphemus*, something that no one had succeeded in doing for many years.” *Id.*, ¶0017. Jain, ¶¶173-175.

By that point, a POSA considering Mizumura’s data on HEK293 produced recombinant Factor C from *Tachypleus tridentatus*, as well as the '498 PCT’s explicit disclosure of production of functional *Limulus polyphemus* recombinant Factor C in HEK293 cells would have reason—including the wide adoption of and reliance upon the LAL test but also including the specificity challenges with that test and the desire to avoid contaminants associated with the natural lysate—to develop a recombinant Factor C protein with a residual activity value similar to that shown in Mizumura’s FIG. 7 **for *Limulus polyphemus*** species of horseshoe crab. Jain, ¶¶176-177.

4. A POSA Would Have Had a Reasonable Expectation of Success in Using *Limulus* Constructs to Generate the HEK293 Produced Recombinant Factor C of Claim 21.

By April 2019, POSAs would have reasonably expected to successfully generate recombinant *Limulus polyphemus* Factor C via HEK293 cells and having a residual activity falling within the range defined in claim 21. Jain, ¶178.

a. Knowledge of the Full Length Amino Acid Sequence Would Have Allowed a POSA to Do a Full Sequence Comparison and Confirm Sufficient Similarity to Reasonably Expect Similar Function.

The '498 PCT describes the successful “obtaining [of] full-length cDNAs encoding all protein factors involved in the coagulation mechanism of *Limulus polyphemus*.” EX1005, ¶¶0017, 0173 (“[*T*]he first successful elucidation of the full-length cDNA sequence (sequence number 1, sequence number 3) encoding a protein that may have *Limulus polyphemus* C factor activity, and the *full-length amino acid sequence of that protein (sequence number 2, sequence number 4)*.”). Having these complete sequences in hand would have allowed a POSA to compare them with gene and amino acid sequences of other, well-studied species such as *Tachypleus tridentatus*, to make reasonable predictions about whether recombinantly-produced proteins would exhibit similar functional characteristics such as “residual activity.” Jain, ¶¶179-180; *see also* EX1010, 38, 48.

While no such comparison could be fully predictive regarding the differences in conservative versus non-conservative mutations between sequences

and their potential impacts on structure and function (as explained above, Section IX.B, *supra*), having both sequences to compare would have provided a POSA with starting information from which a reasonable expectation about the *relative* comparability of residual activity function of *Limulus polyphemus* recombinant Factor C could have been made. EX1010, 48. It would have been within the skill and experience of a POSA as of 2019 to compare amino acid sequences from the then-known *Limulus polyphemus* horseshoe crab and the well-studied *Tachypleus tridentatus* horseshoe crab and, given similarities overall, reasonably expect the two to be comparable in terms of residual activity. Jain, ¶¶181-82.

b. The '498 PCT Describes How to Recombinantly Produce *Limulus Polyphemus* Factor C in a Mammalian Expression System.

The '498 PCT describes the various gene and protein sequences, including “cDNA for a protein having *Limulus polyphemus* factor C activity” (EX1005, ¶0019) from which recombinant protein was generated. *Id.*, ¶¶0020-21; pp. 55-75. The '498 PCT provides a detailed description of how such cDNA sequences were expressed recombinantly. *Id.*, ¶¶0155-185. And the '498 PCT inventors confirmed the endotoxin detecting function of such recombinantly-expressed *Limulus polyphemus* proteins, describing that it was “demonstrated *for the first time* that the use of each of the three recombinant proteins [produced via cDNA from *Limulus polyphemus*] enables quantitative detection of endotoxin with high

sensitivity and high accuracy.” *Id.*, Examples 6-7, ¶¶0178-85. While the ’498 PCT experimental disclosure relates to the CHO mammalian expression system, it would have been well within the skill of a POSA at the time to carry out expression with the also-disclosed HEK293 expression system. For example, Mizumura describes expression of Factor C of the *Tachypleus tridentatus* species of horseshoe crab using **both** the CHO and HEK293 cells. EX1009, ¶¶0282-90 (“(2) Expression of Factor C in Mammalian Cells (CHO DG44)...(3) Expression of Factor C in Mammalian Cells (HEK293)”), 0205-206. Jain, ¶¶183-186.

By 2019, a POSA would have had a reason to recombinantly express the then-elucidated full-length amino acid sequence of *Limulus polyphemus* horseshoe crabs via the HEK293 system as described in Mizumura and would have reasonably expected the resulting proteins to exhibit similar residual activity as those reported in Mizumura for *Tachypleus tridentatus*. Jain, ¶187.

c. The ’318 Patent’s Lead Inventor Testified To A Reasonable Expectation of Success.

Once the sequence information for *Limulus polyphemus* Factor C protein was known, a POSA could have compared such information to that of other known horseshoe crab species and formed a reasonable expectation that the recombinantly produced proteins would exhibit similar residual activity. ’318 patent inventor, Dr. Mizumura, testified to this reasonable expectation as of 2018. Jain, ¶188-189.

In a February 22, 2018 Declaration submitted in support of prosecution *of the '767 Application* (grand-parent application to the '318 patent), Dr. Mizumura provided the then-*recently-determined* amino acid alignment for Factor C as between *Limulus polyphemus* and *Tachypleus tridentatus*. EX1029, 2-4. Dr. Mizumura testified that “a [POSA] would readily recognize that the presently claimed invention could also work when Factor C is the Factor C of *Limulus polyphemus*” and that the “Factor C of *Limulus polyphemus* would also have unexpectedly superior property of being less susceptible to inhibition by ions, as exhibited by Factor C of *Tachypleus tridentatus*.” Ex 1029, 4-5. Jain, ¶190.

In view of Dr. Mizumura’s own testimony over a year before Patent Owner filed the application giving rise to the '318 patent, a POSA would have had a reasonable expectation of success in combining Mizumura and the '498 PCT to generate a recombinant Factor C protein in HEK293 cells with the “residual activity” characteristic recited in challenged claim 21. Jain, ¶191.

B. Ground 2: Claim 21 Is Obvious Over Mizumura In View Of McClymont.

Claim 21 is obvious over Mizumura in view of the 2017 disclosure by McClymont of the full gene coding and amino acid sequences of the *Limulus polyphemus* Factor C protein. As with the '498 PCT, McClymont discloses the full cDNA and amino acid sequence for *Limulus polyphemus* Factor C protein and discloses expressing such protein using several common expression systems

(including yeast and insect cells). EX1010, 84-96, 159-60 (Appx. B). McClymont is not associated with Patent Owner or any inventors. For the same reasons discussed in Section XI.A above, in Ground 1, POSAs would have had reason to utilize the sequence information from McClymont to generate a recombinant Factor C protein of the *Limulus polyphemus* species in HEK293 cells as disclosed for *Tachypleus tridentatus* in Mizumura, and would have reasonably expected the resulting proteins to have residual activity described in Mizumura and falling within the claimed range. For this additional reason, challenged claim 21 is obvious. Jain, ¶¶192.

C. Secondary Considerations Do Not Overcome the Foregoing Demonstration of Obviousness.

Patent Owner offered two declarations from Dr. Mizumura during prosecution arguing that unexpected results associated with the invention rebutted the Examiner's *prima facie* case of obviousness. None of this evidence is probative of the non-obviousness of claim 21. Jain, ¶¶193-95.

1. The January 8, 2021 Mizumura Declaration Does Not Establish Unexpected Results of Claim 21.

Dr. Mizumura's January 8, 2021 declaration was submitted "to explain and demonstrate that [their] invention provides unexpected superior results over" the Examiner's then-pending obviousness rejection. EX1004, 150. Claim 21 had not yet been introduced in prosecution as of the January 8, 2021 declaration. This

declaration introduced new data for recombinantly produced *Tachypleus tridentatus* Factor C (from CHO-S) cells to demonstrate that the CHO DG44 recombinantly produced Factor C performed *better* Factor C expressed in “CHO-S cells, Sf9 cells or HEK cells or native Factor C (TAL).” *Id.*, 150-52. The January 8, 2021 Declaration provides no evidence of unexpected results with respect to the genus of Factor C proteins encompassed by claim 21, both because it was from recombinant Factor C of the *Tachypleus tridentatus* species (not *Limulus polyphemus*) **and** because it was from Factor C recombinantly produced in CHO cells (not HEK293 cells). Jain, ¶¶196-199.

2. The August 11, 2021 Mizumura Declaration Does Not Establish Unexpected Results of Claim 21 Relative to the Closest Prior Art.

In an August 11 Declaration, Dr. Mizumura noted that “[a]s shown in Fig. 7 of the specification, *T. tridentatus* Factor C recombinantly produced by using CHO cell or HEK cell as a host has superior salt tolerance compared to native *T. tridentatus* Factor C (TAL) or *T. tridentatus* Factor C recombinantly produced by using Sf9 [insect] cell as a host.” Ex. 1004, 83. Dr. Mizumura then offered “additional experimental data show[ing] that the same is true in the case of *L. polyphemus* Factor C recombinantly produced by using CHO cell.” *Id.* Claim 21, however, requires *Limulus polyphemus* Factor C recombinantly produced **via HEK293** (not CHO) cells, so the new data offered in Figure 1 of the August 11,

2021 Mizumura Declaration (*id.*, 85) are not relevant to any unexpected properties of the claimed proteins.⁶ See *In re Gartside*, 203 F.3d 1305, 1321 (Fed. Cir. 2000). Jain, ¶¶200-202.

Dr. Mizumura also pointed to a set of “Inhibition data,” cited in a February 3, 2021 IDS. EX1004, 85-86. He argued, based on this data, that “salt tolerance of *Limulus* Factor C produced by HEK 293 cell [mammalian] is superior to LAL and *L. polyphemus* Factor C recombinantly produced by using Sf9 cell [insect] as a host.” *Id.* However, such statement fails to explain how the comparison between the separate “Inhibition data” and the data in Figure 1 (from expression in CHO and Sf9) was made. There is no explanation as to whether the protocols, materials, or methods were similar so as to allow for any valid comparison. Moreover, even if such comparison could be made, it fails to demonstrate any difference *in kind* in “residual activity” (as opposed to a difference of degree). *Galderma Lab’ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013). Jain, ¶¶203-204.

Finally, the ’767 Application disparages native Factor C (LAL) and recombinant Factor C expressed using insect host cells as susceptible to ion inhibition and thus having a low residual activity under such conditions and so, if

⁶ Pending claim 1 recited recombinant expression via CHO DG44 cells *or* HEK293 cells. EX1004, 68. Claim 24 (issued claim 21) recites only HEK293 cells. *Id.*, 73.

anything, a POSA would look to closer prior (e.g., expression in other mammalian cells) for evidence of unexpected results. Jain, ¶205. Petitioner is unaware of any evidence of unexpected results of the Factor C proteins of claim 21 sufficient to rebut the foregoing demonstration of obviousness. Jain, ¶206.

XII. CONCLUSION

Petitioner respectfully requests that the Board institute *inter partes* review and cancel claim 21 of the '318 patent.

Dated: 01-16-2025

Respectfully submitted,
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CERTIFICATE OF SERVICE UNDER 37 C.F.R. § 42.6 (E)(4)

I certify that on January 16, 2025, I will cause a copy of the foregoing document, including any exhibits or appendices filed therewith, to be served via Overnight FedEx at the following correspondence address of record for the patent:

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Date: January 16, 2025

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MacAulay Rush
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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that the foregoing Petition for *Inter Partes* Review contains 13,991 words excluding a table of contents, a table of authorities, Mandatory Notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing. Petitioner has relied on the word count feature of the word processing system used to create this paper in making this certification.

Date: January 16, 2025

/MacAulay Rush/
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