

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHARLES RIVER LABORATORIES, INC.,

Petitioner,

v.

SEIKAGAKU CORPORATION,

Patent Owner.

Case No. IPR2025-00440

Patent No. 11,236,318

PATENT OWNER'S DISCRETIONARY DENIAL BRIEF

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TABLE OF EXHIBITS

<u>Exhibit No.</u>	<u>Description</u>
2001	Excerpt from U.S. Application No. 14/650,767 File History – Claims dated June 9, 2015
2002	Excerpt from U.S. Application No. 14/650,767 File History – Non-Final Rejection dated September 16, 2016
2003	FAQs for Interim Processes for PTAB Workload Management, <i>available at</i> https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management
2004	Declaration of Michael A. Frohman, M.D., Ph.D. and exhibits from Opposition for European Patent No. 3530670
2005	Notice of Opposition to European Patent No. 3441466
2006	Notice of Opposition to European Patent No. 3530670
2007	Extract from the Register of European Patents for European Patent No. 4291648
2008	Ding, et al., “Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ,” Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in Opposition to European Patent No. 3441466
2009	Ding, et al., “Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ,” Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 17/650,803
2010	Ding, et al., “Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ,” Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 18/275,777

2011	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> , Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 18/953,525
2012	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in Opposition to European Patent No. 3530670
2013	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in Opposition to European Patent No. 3441466
2014	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 17/650,803
2015	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 18/275,777
2016	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 18/953,525
2017	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in Opposition to European Patent No. 3441466
2018	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 17/650,803
2019	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 18/275,777

2020	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 18/953,525
2021	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in Opposition to European Patent No. 3441466
2022	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 17/650,803
2023	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 18/275,777
2024	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 18/953,525
2025	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in Opposition to European Patent No. 3441466
2026	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 17/650,803
2027	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 18/275,777

2028	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 18/953,525
2029	Tokunaga, 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," (1991) J. Biochem, 109: 150-157, submitted in Opposition to European Patent No. 3441466
2030	Tokunaga, 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," (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 17/650,803
2031	Tokunaga, 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," (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 18/275,777
2032	Tokunaga, 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," (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 18/953,525
2033	D19 submitted in Opposition to European Patent No. 3441466
2034	U.S. Publication No. 2023/0258647

Pursuant to the Patent Office's March 26, 2025 Memorandum titled "Interim Process for PTAB Workload Management" ("Memorandum"), Patent Owner Seikagaku Corporation ("Seikagaku" or "Patent Owner") respectfully requests that the Director exercise discretion and deny institution of Petitioner Charles River Laboratories, Inc.'s ("Petitioner" or "CRL") Petition for *inter partes* review ("IPR") of Claim 21 of U.S. Patent No. 11,236,318 ("'318 Patent").

I. INTRODUCTION

Numerous factors support the Director discretionarily denying institution.

First, the success of Petitioner's prior art unpatentability challenge hinges on its priority date attack under 35 U.S.C. § 112. But Petitioner rehashes ***substantially the same*** arguments that the United States Patent and Trademark Office ("PTO") considered during prosecution of the '318 Patent and the related U.S. Application No. 14/650,767 ("'767 Application"). This alone strongly favors discretionary denial under 35 U.S.C. § 325(d).

Second, analyzing Petitioner's unpatentability arguments would require the Board to devote its limited resources to assess the Petition's heavily expert-driven unpatentability analysis of only ***one of 21 claims*** in a patent that issued ***years ago***. The inefficiencies associated with assessing a single claim and the multi-year existence of the patent further support discretionary denial.

Third, expert opinions presented during a European Opposition proceeding involving Patent Owner's European patent conflict with Petitioner's substantive arguments and undermine the strength of Petitioner's arguments. Further, substantial evidence supports the conclusion that Petitioner filed that European Opposition and thus sanctioned arguments that directly contradict arguments in the Petition.

Accordingly, as explained below, the Director should discretionarily deny institution.

II. THE '318 PATENT

Filed on April 30, 2019, the application that led to the '318 Patent is a continuation of Application No. 15/983,725, filed on May 18, 2018, now Pat. No. 10,982,202, which is a continuation of Application No. 14/650,767, filed as Application No. PCT/JP2013/083082 on **December 10, 2013**, now Pat. No. 10,144,923. The '318 Patent also claims foreign priority to JP 2012-269840, filed December 10, 2012.

A. Claim 21

Claim 21, the sole claim at issue, 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.

Ex. 1001 at cl. 21.¹

This claim captures the essence of the inventors' contribution to the field: successful recombinant production of Factor C in a mammalian cell (e.g., a HEK293 cell) that exhibits less susceptibility to inhibition in the presence of ions.

B. Specification of the '318 Patent

The '318 Patent describes the "Factor C of the present invention" as having "low susceptibility to inhibition of activity by an ion," which refers to "the state that the Factor C of the present invention *exhibits a high residual activity in the presence of an ion, as compared with a control Factor C.*" Ex. 1001 at 17:20-25. The '318 Patent specifically teaches how to quantify whether the recombinant Factor C demonstrates this inventive "low susceptibility to inhibition of activity by an ion" by (i) explaining how to determine the residual activity and (ii) providing minimum

¹ Emphasis added unless otherwise noted.

threshold values in specific salt concentrations for the residual activity. Ex. 1001 at 17:53-18:15. Specifically, the '318 Patent states:

Specific examples of 'low susceptibility to inhibition of activity by an ion' further include such a property that the Factor C of the present invention exhibits a ***residual activity of 10% or higher*** or 20% or higher ***in the presence of 21 mM sodium citrate***, as compared with the control Factor C . . . ; such a property that the Factor C of the present invention exhibits a ***residual activity of 15% or higher*** or 25% or higher ***in the presence of 16 mM magnesium sulfate***, as compared with the control Factor C. . . . The Factor C of the present invention may have any one of the above properties singly or two or more of the above properties in combination. 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."

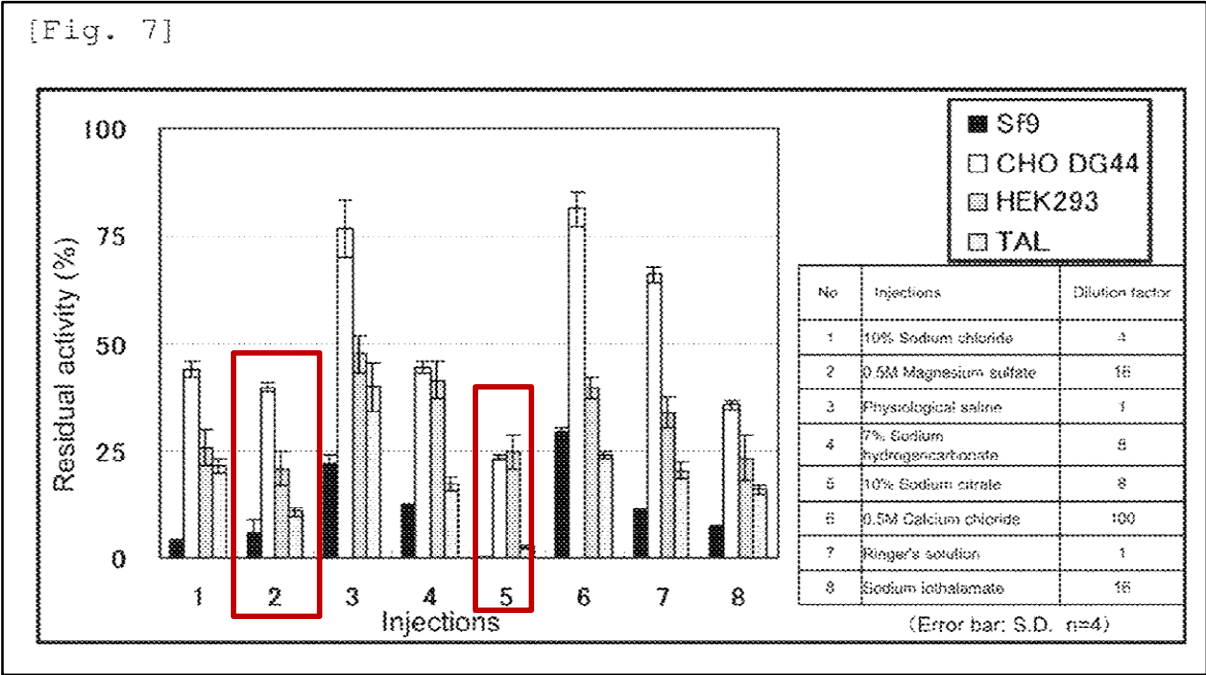
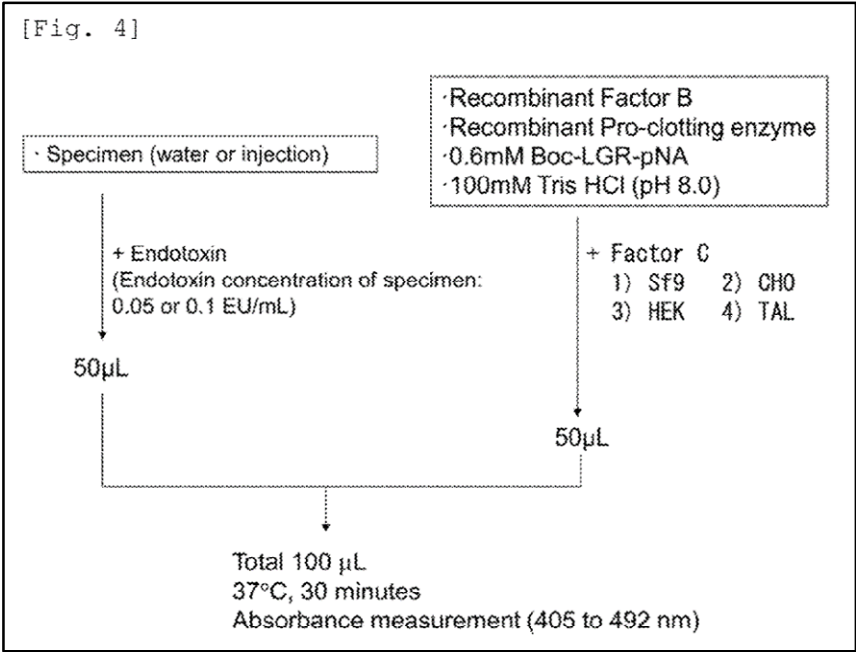
Id.

Thus, Claim 21 recites specific examples described in the specification that demonstrate the inventive feature of the recombinant Factor C having low susceptibility to inhibition of activity by an ion. Indeed, Petitioner's expert notes

that “residual activity” captures the concept of mitigating reaction inhibition in the presence of an ion. Ex. 1002 ¶ 43.

The specification also describes the preparation of Factor C using HEK293 cells as the host cell and measuring the inhibition of activity of the Factor C in the presence of salt ions. Ex. 1001 at 31:14-43, 34:39-35:43. Figure 4 shows the procedure by which activity of Factor C was measured, and Figure 7 shows that expressing Factor C in HEK293 cells leads to low susceptibility to inhibition of activity by an ion, including in the presence of the claimed salt solutions (*i.e.*, 21 mM sodium citrate and 16 mM magnesium sulfate).² Ex. 1001 at 35:20-21, 35:26-43, Figs. 4, 7.

² As the specification explains, an 8-fold dilute of 10 w/v% sodium citrate injection yields a final sodium concentration of about 21 mM, and a 16-fold dilute of 0.5 M magnesium sulfate injection yields a final magnesium sulfate concentration of about 16 mM. Ex. 1001 at 35:4-7, 15-17.



Ex. 1001 at Figs. 4, 7 (annotated).

C. Relevant File History of the '318 Patent

On June 30, 2020, the PTO issued a Non-Final Rejection under various 35 U.S.C. § 112 grounds, including rejecting then-pending claims 2-9, 12, and 13 for lack of written description. Ex. 1004 at 371-373.

Then-pending independent claim 2 and dependent claim 8 recited:

2. A Factor C protein having activity of Factor C,

wherein the Factor C protein comprises an amino acid sequence selected from the group consisting of:

(A) the amino acid sequence of SEQ ID NO: 2;

(B) an amino acid sequence having 90% or higher sequence identity to the amino acid sequence of SEQ ID NO: 2, and having activity of Factor C;

(C) the amino acid sequence of SEQ ID NO: 4; and

(D) an amino acid sequence having 90% or higher sequence identity to the amino acid sequence of SEQ ID NO: 4, 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.

8. The Factor C protein according to claim 2, which exhibits a residual Factor C activity of 15% or higher in the presence of 16 mM magnesium sulfate.

Ex. 1004 at 515-516. Notably, SEQ ID NO: 2 corresponds to the amino acid sequence of Factor C derived from the *Tachypleus tridentatus* horseshoe crab, and SEQ ID NO: 4 corresponds to the amino acid sequence of Factor C derived from the *Carcinoscorpius rotundicauda* horseshoe crab. Ex. 1001 at 13:39-41, 43-45.

The PTO asserted that claim 2 (i) lacked ***insufficient representative species***; and (ii) “[o]ther than a recombinant *Tachypleus tridentatus* or *Carcinoscorpius rotundicauda* Factor C protein expressed in [CHO] or [HEK] cells, which Factor C protein has Factor C activity and contains (α -2, 3)-linked terminal sialic acid in a greater amount as compared with corresponding native horseshoe crab Factor C protein and/or a corresponding horseshoe crab Factor C protein, there is ***no disclosed or art-recognized correlation between the structure of the recited Factor C protein and the characteristic of residual activity of 10% or higher in the presence of 21 mM sodium citrate and the additional characteristics recited in claims 3-9.***” Ex. 1004 at 374-376.

On September 17, 2020, Applicant responded to the written description rejection by submitting a declaration from Dr. Hikaru Mizumura, one of the inventors of the '318 Patent. Ex. 1004 at 243-248. Among other things, Dr. Mizumura presented the below table in his declaration listing the amino acid sequence identity of Factor C derived from each of (i) *Tachypleus tridentatus* (Tt), (ii) *Carcinoscorpius rotundicauda* (Cr), and (iii) *Limulus polyphemus* (Lp):

(Table 1) Amino acid sequence identity of three types of Factor Cs	
Factor C between	Identity (%)
Tt and Cr	$990 / 1019 * 100 = 97.2$
Tt and Lp	$936 / 1020 * 100 = 91.8$
Lp and Cr	$926 / 1020 * 100 = 90.8$

Ex. 1004 at 245.

On October 8, 2020, the PTO issued a Final Rejection, which withdrew the Section 112 grounds and only raised obviousness grounds. Ex. 1004 at 183-203. The Applicant and PTO subsequently went back-and-forth with the PTO issuing a Non-Final Rejection on March 9, 2021. Ex. 1004 at 99-116. In response, Applicant submitted an interview agenda for a phone interview with the PTO, which included new claim 24 that ultimately issued as Claim 21. Ex. 1004 at 96-98. After the interview, Applicant amended its claims to include claim 24 and presented another declaration from Dr. Mizumura demonstrating the superior salt tolerance results for *Limulus polyphemus* Factor C expressed by HEK293 cells. Ex. 1004 at 67-87. The PTO subsequently allowed the claims, noting that unexpected results existed to rebut the *prima facie* case of obviousness. Ex. 1004 at 21-24.

III. DISCRETIONARY DENIAL IS WARRANTED

A. Institution Should be Denied under Section 325(d)

Petitioner asserts that Claim 21 is not entitled to its earliest priority date because the priority '767 Application does not provide written description support or enable the full scope of the claim. Pet. at 22-41. But during prosecution of the '318 Patent and the parent '767 Application, the PTO considered (and ultimately withdrew) substantially the same written description support and enablement arguments.

Given that none of the art Petitioner relies on for unpatentability qualifies as prior art unless Petitioner succeeds with its priority date challenge, the overlap in Section 112 arguments presented by Petitioner and previously considered by the PTO warrants discretionary denial under 35 U.S.C. § 325(d). Section 325(d) provides that “the Director may take into account whether, and *reject the petition* or request *because*, the *same or substantially the same* prior art or *arguments previously were presented to the Office*.”

The Section 325(d) analysis applies a two-prong framework: (i) whether the arguments presented in the petition are the same or substantially the same as those previously presented to the PTO; and (ii) if so, whether the petitioner has demonstrated a material error by the PTO in its prior consideration of those arguments. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*,

No. IPR2019-01469, Paper 6 (“*Advanced Bionics*”) at 8 (P.T.A.B. Feb. 13, 2020) (precedential). Here, both prongs support discretionary denial.

1. The Petition Meets the First Prong of the *Advanced Bionics* Test

Petitioner argues that the full scope of Claim 21 lacks written description support and is not enabled by the specification of the '767 Application—an earlier application in the priority chain. Pet. at 22-41. Petitioner's Section 112 arguments, however, are substantially the same as those the PTO considered during prosecution of the '318 Patent and the '767 Application.

a. The PTO Considered Substantially the Same Written Description Arguments During Prosecution of the '318 Patent

As discussed in Section II.C, incorporated here, during prosecution of the application that led to the '318 Patent, the PTO rejected then-pending claims 2 and 8 under 35 U.S.C. § 112(a) for lack of written description support.³ Ex. 1004 at 367,

³ As Petitioner acknowledges, the specification of the '767 Application and '318 Patent are identical. Pet. at 21-22.

371-373. The table below compares then-pending claims 2 and 8 with Claim 21 of the '318 Patent. Similar limitations have been identified in the same text color⁴:

Then-Pending Claims 2 and 8 During '318 Prosecution	Claim 21 of the '318 Patent
2. A Factor C protein having activity of Factor C, wherein the Factor C protein comprises an amino acid sequence selected from the group consisting of: (A) the amino acid sequence of SEQ ID No: 2; (B) an amino acid sequence having 90% or higher sequence identity to the amino acid sequence of SEQ ID NO: 2, and having activity of Factor C; (C) the amino acid sequence of SEQ ID NO: 4; and (D) an amino acid sequence having 90% or higher sequence identity to the amino acid sequence of SEQ ID NO: 4, 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	A horseshoe crab Factor C protein having activity of Factor C, wherein the horseshoe crab is <i>Limulus polyphemus</i>, 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.

⁴ As noted during prosecution, *Limulus polyphemus* Factor C shares more than 90% sequence identity with SEQ ID Nos. 2 and 4 and thus fell within the scope of then-pending claim 2. Ex. 1004 at 245.

wherein the Factor C protein exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate. 8. The Factor C protein according to claim 2, which exhibits a residual activity of 15% or higher in the presence of 16mM magnesium sulfate.	
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As seen in the table, the claims rejected by the PTO for lack of written description support have overlapping subject matter with Claim 21. The PTO asserted that these claims lacked written description because the specification failed to describe (i) sufficient representative species or (ii) structural features common to the claimed genus. Ex. 1004 at 367, 371-373.

In particular, the PTO argued that the specification failed to disclose sufficient representative species “of the recited genus of recombinant horseshoe crab Factor C polypeptides that exhibit a residual activity of 10% or higher in the presence of 21 mM sodium citrate.” Ex. 1004 at 374. It further asserted that “there is no disclosed or art-recognized correlation between the structure of the recited Factor C protein and the characteristic of residual activity of 10% or higher in the presence of 21 mM sodium citrate and the additional characteristics recited in claims 3-9.” Ex. 1004 at 375-376.

Petitioner rehashes substantially the same written description arguments here. Pet. at 22-31. It asserts that insufficient representative species exist to demonstrate

possession of the full scope of the claimed genus, noting that the specification only describes HEK-produced *Tachypleus tridentatus* recombinant Factor C protein with the claimed residual activity. Pet. at 23-24. It further asserts that the specification fails to describe structural features common to the members of the genus that correlate with the claimed residual activity. Pet. at 29-31.

Petitioner's attempt to overcome the first prong of the *Advanced Bionics* test fails for two reasons.

First, Petitioner argues that “the genus defined by the claim considered by the Examiner (as-filed claim 2) did encompass at least some representative species . . . which is ***not*** the case for any argument made in this Petition.” Pet. at 16. But even if the PTO ***ultimately*** believed some representative species existed for then-pending claim 2, it still ***rejected*** that claim for lack of written description support due to insufficient representative species. Ex. 1004 at 371-376. Thus, the PTO considered substantially the same argument that the Petitioner makes here—*i.e.*, alleged lack of sufficient representative species to demonstrate written description.

Second, Petitioner asserts that 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.”⁵ Pet. at 16. The PTO, however, did not state that it withdrew the Section 112 rejection because of the amendment, let alone explain why it did so. See Ex. 1004 at 185-203. In short, Petitioner's assertion is sheer speculation. See *Guardant Health, Inc. v. Univ. of Wash.*, No. IPR2022-00449, Paper 13 at 18 (P.T.A.B. Aug. 1, 2022) (declining to find PTO materially erred in finding written description support and noting that speculation is not evidence). In any event, regardless of **why** the PTO withdrew the rejection, Petitioner still presents **substantially the same arguments** the PTO previously considered.

b. The PTO Considered Substantially the Same Written Description and Enablement Arguments During Prosecution of the '767 Application

Petitioner also presents substantially the same arguments that the PTO considered during prosecution of the priority '767 Application, which further supports discretionary denial under Section 325(d). See, e.g., *Passage Bio, Inc. v.*

⁵ Petitioner defines the “Greater Sialic Acid Limitation” as “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.” Pet. at 12.

The Trustees of the Univ. of Penn., No. PGR2021-00073, Paper 13 at 26 (P.T.A.B. Oct. 6, 2021) (“Having reviewed the prosecution histories, however, we find that Petitioner’s arguments are the same or substantially the same as those previously presented to the Office during the prosecution of the ’218 application **and the priority applications.**”).

Specifically, during prosecution, the PTO rejected then-pending claims 43 and 47 for lack of written description and enablement. The table below compares then-pending claims 43 and 47 of the ’767 Application with Claim 21 of the ’318 Patent. *Compare* Ex. 2001 at 1 *with* Ex. 1001 at cl. 21. Similar limitations have been identified in the same text color:

<u>Then-Pending Claims 43 and 47 During ’767 Application</u>	<u>Challenged Claim 21 of the ’318 Patent</u>
43. A horseshoe crab Factor C having activity of Factor C.	A horseshoe crab Factor C protein having activity of Factor C,
47. The Factor C according to claim 43, which exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate.	wherein the horseshoe crab is <i>Limulus polyphemus</i> , 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.
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As the table shows, the claims rejected by the PTO for lack of written description and enablement have overlapping subject matter with Claim 21. The PTO asserted that these claims failed to comply with the written description requirement because “one of skill in the art would not accept the disclosure of Factor C isolated from *Tachypleus tridentatus* or *Carcinoscorpius rotundicauda* hemocyte lysate and *Tachypleus tridentatus* Factor C expressed in Sf9 insect cells, CHO cells, or HEK cells as being representative of all other horseshoe crab Factor C polypeptides as encompassed by the claims.” Ex. 2002 at 9.

Petitioner rehashes substantially the same written description arguments here. Pet. at 22-31. Petitioner asserts that insufficient representative species exist to demonstrate possession of the full scope of the claimed genus, arguing that the specification only describes a HEK-produced *Tachypleus tridentatus* recombinant Factor C protein with the claimed residual activity. Pet. at 23-24.

The PTO also rejected claims 43 and 47 of the '767 Application for lack of enablement. The PTO explained that “because the specification, while being enabling for Factor C isolated from *Tachypleus tridentatus* or *Carcinoscorpius rotundicauda* hemocyte lysate and *Tachypleus tridentatus* Factor C expressed in Sf9 insect cells, CHO cells, or HEK cells, does not reasonably provide enablement for

all horseshoe crab Factor C polypeptides as encompassed by the claims.” Ex. 2002 at 10.

As part of this lack of enablement rejection, the PTO addressed similar *Wands* factors as the Petitioner: (i) nature of the invention; (ii) breadth of the claims; (iii) state of the prior art; (iv) level of one of ordinary skill; (v) level of predictability in the art; (vi) amount of direction provided by inventor; and (vii) working examples. *Compare* Ex. 2002 at 10-15 *with* Pet. at 37-42.

Accordingly, the Petition meets the first prong of the *Advanced Bionics* test.

2. The Petition Meets the Second Prong of the *Advanced Bionics* Test

Petitioner cannot demonstrate that the Examiner erred, let alone erred in a manner material to patentability, when he previously considered and rejected substantially the same arguments as Petitioner raises here.

Petitioner nowhere addresses the lack of written description and enablement arguments raised during prosecution of the '767 Application. On this basis alone, the Director should deny institution. *See, e.g., Ivantis, Inc. v. Sight Sci., Inc.*, No. IPR2022-01540, Paper 14 at 14 (P.T.A.B. March 22, 2023) (“Petitioner bears the burden to ‘demonstrate[] that the Office erred in a manner material to the patentability of challenged claims.’”); *Vital Connect Inc. v. Bardy Diagnostics, Inc.*, No. IPR2023-00381, Paper 7 at 19-20 (P.T.A.B. July 11, 2023) (denying institution

where petition is “silent on material error”).⁶ As the Board stated in *Advanced Bionics*, “[i]f a condition in the first part of the framework is satisfied and the petitioner fails to make a showing of material error,” then “the Director generally will exercise discretion not to institute *inter partes* review.” *Advanced Bionics* at 8-9.

While Petitioner addresses the lack of written description arguments made during prosecution of the application that led to the '318 Patent, its argument as to “material error” fails to withstand scrutiny. Petitioner argues that the “Examiner materially erred by failing to re-lodge the prior § 112 rejection when Patent Owner introduced [Claim 21].” Pet. at 18. But this argument fails to explain *why* or *how* the Examiner erred in a manner material to patentability.

Petitioner also asserts that “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” and thus, “[t]o the extent the Examiner relied upon [information presented in the Mizumura

⁶ Petitioner filed the Petition on January 16, 2025, which is before the PTO issued the Memorandum. As such, Petitioner should have addressed discretionary denial issues, including any alleged material error by the PTO, in its Petition.

declaration] to establish the inventors' possession of the functionally-claimed recombinant *Limulus polyphemus* Factor C proteins as of December 10, 2012, such was material error." Pet. at 18.

But, as discussed, the PTO did not explain why it withdrew the lack of written description argument during prosecution of the '318 Patent. Petitioner cannot argue material error based on *speculation* that the Mizumura declaration factored into the PTO's decision, let alone based on speculation as to what portions of the declaration the PTO *may* have considered when withdrawing the rejection. *See, e.g., Ivantis, Inc. v. Sight Sci., Inc.*, No. IPR2022-01540, Paper 14 at 14 (P.T.A.B. March 22, 2023) (declining to equate silence by the examiner to material error).

Finally, Petitioner argues that the PTO materially erred in failing "to consider written description and/or enablement in analyzing the facial priority claim of the ['318 Patent] to determine whether Claim 21 was entitled to the December 10, 2012 priority date." Pet. at 18-19. Yet the record shows the PTO *did* consider written description during the '318 Patent's prosecution and considered written description and enablement during prosecution of the related '767 Application. Ex. 1004 at 367, 371-373; Ex. 2002 at 5-15. That "reasonable minds can disagree regarding the purported treatment of the . . . arguments" does not mean that it can "be said that the Office erred in a manner material to patentability." *Advanced Bionics* at 9 (cleaned up).

For this reason alone, the Director should exercise its discretion under Section 325(d) and deny institution.

B. Additional Discretionary Factors Favor Denial of Institution

Additional factors also support discretionary denial. As outlined in the Memorandum, “relevant considerations” can include (i) the length of time the claims have been in force; (ii) the extent of the petition’s reliance on expert testimony; and (iii) the strength of the unpatentability challenge. Memorandum at 2. The Memorandum further explains that the Director “will also consider the ability of the PTAB to comply with pendency goals for . . . its statutory deadlines for AIA proceedings, and other workload needs” with one aim being “to improve PTAB efficiency.” Memorandum at 3.

1. Length of Time Claims Have Been in Force and Efficiency Concerns Favor Discretionary Denial

The '318 Patent issued on February 1, 2022 and thus has been in force for years. Ex. 1001. Given the multi-year period that Claim 21 has been in force, Petitioner’s delay in filing its Petition favors discretionary denial. Moreover, Petitioner elected to challenge only *one* of the '318 patents' 21 claims. This decision further supports discretionary denial as it contravenes the Memorandum’s aim of improving efficiency by asking the Board to expend valuable resources to evaluate the patentability of a single claim.

2. Reliance on Expert Testimony and Strength of Statutory Unpatentability Grounds Further Favors Discretionary Denial

The Petition's heavy focus on expert testimony and reliance on Section 112 arguments further support discretionary denial. As 35 U.S.C. § 311(b) states, "[a] petitioner in an inter partes review may request to cancel as unpatentable 1 or more claims of a patent *only on a ground that could be raised under section 102 or 103* and only on the basis of prior art consisting of patents or printed publications." Petitioner does not rely on any references that qualify as prior art if it loses its Section 112-based priority date arguments.

Moreover, Petitioner heavily relies on an expert declaration to support its lack of written description and enablement arguments. Pet. at 22-42; *see also* Ex. 1002. As discussed in the FAQs for Interim Processes for PTAB Workload Management, "[w]hile the Board may consider expert testimony, as a matter of efficiency, extensive reliance on expert testimony . . . may suggest that the questions are better resolved in an Article III court." Ex. 2003 at 6. The Petition's extensive reliance on expert testimony for its priority date argument thus favors discretionary denial.

Weaknesses in Petitioner's unpatentability challenge also support discretionary denial. The evidence strongly suggests that Petitioner presented positions in a European Opposition proceeding involving Patent Owner's European Patent No. 3530670 ("EP '670") that contradict its positions here. *See infra*, Section

III.B.2.a. Further, even if Petitioner did not instigate the EP '670 Opposition proceeding, expert testimony there rebuts Petitioner's priority date arguments.

As discussed, Petitioner asserts that Claim 21 is not enabled by the priority '767 Application because a POSA would have needed to unduly experiment to discover and characterize *Limulus polyphemus* Factor C and recombinantly express it in HEK293 cells. In the EP '670 Opposition, however, the patent challenger submitted a declaration from Michael A. Frohman, M.D., Ph.D.—an expert in “biochemistry, immunology, developmental and molecular biology, with **38 years of experience** in molecular cloning”—that tells a very different story. Ex. 2004 ¶ 2.

In his declaration, Dr. Frohman opines on a number of “questions from the perspective of a [POSA] charged with the determination of the full-length *Limulus* Factor C sequence **before October 18, 2016,**” including whether it would have been difficult to obtain the cDNA sequence of *Limulus polyphemus* and express it after the sequence had been obtained. Ex. 2004 ¶ 5 (emphasis in original). Dr. Frohman provides numerous reasons why a POSA would have been able to do these things with little difficulty.

First, to obtain the cDNA sequence of *Limulus polyphemus*, Dr. Frohman explains a POSA “would have most likely used Rapid Amplification of cDNA Ends (RACE) to obtain the sequence of the cDNA encoding Factor C from *Limulus polyphemus*.” Ex. 2004 ¶ 7. Although he focuses his analysis on what a POSA

would have known in 2016, Dr. Frohman points to publications and knowledge available well before 2013.

Dr. Frohman explains that he developed RACE in **1988** “as a quick approach to obtain full-length cDNA sequences in cases where a partial stretch of the mRNA sequence was known” and that it “can be used to obtain a full-length cDNA sequence *in a matter of days.*” Ex. 2004 ¶ 8. He also states that it would “have been entirely straightforward for the skilled person to design RACE primers based on the available *Limulus* sequence information listed in items (i)-(iii) above.” *Id.* ¶ 10. Notably, item (iii) referenced in Dr. Frohman’s declaration is a 1991 Tokunaga publication noting that Dr. Tokunaga and his colleagues had isolated and characterized Factor C protein from the *Limulus polyphemus* species of horseshoe crab and compared its properties to Factor C from the *Tachypleus tridentatus* horseshoe crab. Ex. 1022 at 150, 155.

Second, Dr. Frohman explains that a POSA could have also used protocols described in publications from the 1990s to obtain the cDNA sequence for *Limulus polyphemus*. Ex. 2004 ¶¶ 11-16. Relying on U.S. 5,716,834, published in **1998** (Ex. 1012), and Ding in **1995** (Ex. 2012), Dr. Frohman opines that obtaining the sequence was “very straightforward” such that the “approach [used in these references] would have been successful to obtain the *Limulus* Factor C cDNA” with “no reason to expect any technical difficulties for repeating this protocol for *Limulus*.” Ex. 2004 ¶ 14.

After obtaining the cDNA sequence of *Limulus polyphemus*, as Dr. Frohman explains, a POSA could have expressed it with routine experimentation. Ex. 2004 ¶¶ 44-48. He explains that “the cDNA sequence of the *Limulus* Factor C is very similar to the other known species of horseshoe crabs, which had been successfully expressed in Sf9, CHO DG44 and HEK 293 cells,” pointing to “D1 ('241).” *Id.* ¶ 45. Notably, D1 refers to EP 2930241, filed December 10, 2013, which is in the same family as the '767 Application and the '318 Patent. According to Dr. Frohman, by following the “example of **D1** using the *Limulus* sequence,” he would “not anticipate experiencing any difficulties.” *Id.* ¶ 47.

As such, contrary to Petitioner's arguments here, a POSA **would not** have had to conduct undue experimentation to discover and characterize the gene and amino acid sequence for *Limulus polyphemus* Factor C and recombinantly express it in HEK293 cells, as required by Claim 21. The weakness of Petitioner's priority date arguments, which it **must** succeed on for any of the underlying references to be considered prior art, further favors discretionary denial.

a. Substantial Evidence Indicates that the Frohman Declaration in the European Opposition was Submitted on Behalf of Petitioner

While the identity of the party that filed the Opposition and sponsored Dr. Frohman's Declaration in EP '670 is not disclosed, the evidence strongly indicates

that Petitioner did so, which further supports the Director discretionarily denying institution.

Sandra Pohlman from the law firm df-mp Dörries Frank-Molnia & Pohlman submitted the Opposition in EP '670. Ex. 2006 at 1. Ms. Pohlman also submitted an Opposition against PO's European Patent No. EP3441**466** ("EP '466"), which is in the same patent family as the '318 Patent. Ex. 2005. She also currently handles prosecution for Petitioner's European Patent Application EP4291648, as she is listed as the "Representative(s)." Ex. 2007.

As part of the Opposition in EP '670, Ms. Pohlman and her firm submitted document D24 by Jeak Ding and M. Anthony A. Navas III entitled "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, *Carcinoscorpius rotundicauda*" ("*Ding*") (Ex. 2012) that included a watermark from her firm along with a unique identifier "COM04X01498" (reproduced below).

Molecular Marine Biology and Biotechnology (1995) 4(1), 90–103

Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, *Carcinoscorpius rotundicauda*

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Abstract

Two forms of Factor C cDNAs: CrFC21 (3448 bp) and CrFC26 (4182 bp) have been cloned into λ gt22. CrFC26 includes 568 nucleotides of 5' untranslated region (5' UTR) containing seven ATGs before the real initiation site, an open reading frame (ORF) of 3249 nucleotides, a stop codon, and 365 nucleotides of 3' untranslated sequence. There are four polyadenylation signals and six potential glycosylation sites. The ORF codes for a signal peptide of 24 amino acids and a Factor C zymogen of 1059 residues. The CrFC21 lacks most of the 5' UTR, and has some base changes in its ORF. The predicted secondary mRNA structures of the 5' end of CrFC26 showed numerous stem-and-loop structures, thus obscuring its real start codon. In contrast, CrFC21 has a well-exposed AUG start site, and expresses Factor C in transcription-translation reactions in vitro. There is a typical serine protease catalytic triad of Asp-His-Ser, which is structurally like prothrombin, but catalytically more similar to trypsin. Although an overall homology of 97.7% was observed in comparison with the *Tachypleus tridentatus* Factor C (TtFC) cDNA, there were notable differences in the restriction sites and subtle base substitutions in the CrFC cDNA. The high degree of homology between Factor C from *T. tridentatus* and *C. rotundicauda* substantiates, at the molecular level, the proximity of these two species in the course of evolution. This finding contravenes the apparent disparities with respect

to their morphology, ecological habitat, and taxonomical classification.

Introduction

There are four extant species of horseshoe crabs: *Limulus polyphemus*, *Tachypleus tridentatus*, *Tachypleus gigas*, and *Carcinoscorpius rotundicauda*. Within the predominant type of blood cell, amoebocytes, are enzymes belonging to the family of serine proteases that sequentially undergo limited proteolysis (Iwanaga et al., 1985) upon endotoxin activation to finally convert coagulogen into an insoluble gel, coagulin (Solum, 1973). This cascade of enzymes and coagulogen constitutes the commercially available amoebocyte lysate used for detecting endotoxin. The latter is extremely ubiquitous and indomitable, contaminating parenteral preparations, water, food, and pharmaceutical products. The *Limulus* amoebocyte lysate (LAL) is a rapid and sensitive in vitro assay for detecting femtogram levels of endotoxin (Ho, 1983).

The elucidation of the molecular events that are responsible for the subsequent gelation of the amoebocyte lysate was attributed to the isolation and characterization of the serine proteases from either *L. polyphemus* or *T. tridentatus*. These include Factor C (Nakamura et al., 1986) and proclotting enzyme (Nakamura et al., 1985). However, to date, there is a lack of information on similar enzymes from their mud-dwelling Southeast Asian counterpart, *C. rotundicauda*, except our recent reports on purification and characterization of its Factor C enzyme (Navas et al., 1990; Ding et al., 1993a; Ho et al., 1993).

Factor C is the endotoxin-sensitive intracellular serine protease zymogen that initiates the coagulation cascade system. It exists as single- and double-chain forms in *C. rotundicauda* (Ding et al., 1993a). While the catalytic site of the molecule is found in the light chain, the endotoxin-binding site is located at the NH₂-terminal heavy chain region (Nakamura et al., 1988). Muta et al. (1991) have cloned the *T. tridentatus* Factor C, albeit in two partial overlapping fragments: pFC 41 and pFC 53, henceforth re-

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Kopie von subito e.V., geliefert für df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB (COM04X01498)

Ex. 2012 at 1 (annotated).

The *exact same watermark and unique identifier* appear in a copy of *Ding* submitted by Petitioner during prosecution of its U.S. Application Nos. 17/650,803 (Ex. 2009); 18/275,777 (Ex. 2010); and 18/953,525 (Ex. 2011), and they also appear in the copy of *Ding* submitted with the Opposition in EP '466 (Ex. 2008). That a document with the same watermark and unique identifier appears not only in the Opposition of EP '670 but also in the file histories of applications prosecuted by Petitioner, as well as in the Opposition of EP '466, strongly suggests that Petitioner is involved in the EP '670 Opposition proceedings and thus commissioned Dr. Frohman's declaration.

Further supporting this conclusion, as the table below shows, Ms. Pohlman and her firm not only submitted the same copy of *Ding* across these proceedings, but they also submitted *four other references* in the Opposition in EP '466 that have *identical markings* (e.g., watermarks, translations, handwritten notations) to documents filed by Petitioner as part of prosecution for U.S. Application Nos. 17/650,803; 18/275,777; and 18/953,525:

Document	Matching characteristics	Filed in	Filed by
Wang et. al. 2002	Vertical watermark: "Downloaded from [website] by guest on March 28, 2020"	Opposition of EP '466 (Ex. 2013)	df-mp Dörries Frank- Molnia & Pohlman

		U.S. App. No. 17/650,803 ⁷ (Ex. 2014)	Petitioner
		U.S. App. No. 18/275,777 (Ex. 2015)	Petitioner
		U.S. App. No. 18/953,525 (Ex. 2016)	Petitioner
Hossler et. al. 2009	Vertical watermark: “Downloaded from [website] by guest on 30 March 2020”	Opposition of EP ‘466 (Ex. 2017)	df-mp Dörries Frank- Molnia & Pohlman
		U.S. App. No. 17/650,803 (Ex. 2018)	Petitioner
		U.S. App. No. 18/275,777 (Ex. 2019)	Petitioner
		U.S. App. No. 18/953,525 (Ex. 2020)	Petitioner

⁷ Wang filed in U.S. Application No. 17/650,803 (Ex. 2014) also bears the same “D3” notation in the top right as Wang filed in the EP ‘466 Opposition (Ex. 2013).

Koshiha et al. 2007	Vertical watermark: “Downloaded from [website] by guest on December 18, 2014”	Opposition of EP ‘466 (Ex. 2021)	df-mp Dörries Frank- Molnia & Pohlman
		U.S. App. No. 17/650,803 (Ex. 2022)	Petitioner
		U.S. App. No. 18/275,777 (Ex. 2023)	Petitioner
		U.S. App. No. 18/953,525 (Ex. 2024)	Petitioner
Hashiguchi et al., 2008	English machine translation of the corresponding Japanese article	Opposition of EP ‘466 (Ex. 2025)	df-mp Dörries Frank- Molnia & Pohlman
		U.S. App. No. 17/650,803 ⁸	Petitioner

⁸ Hashiguchi filed in U.S. Application No. 17/650,803 (Ex. 2026) also bears the same “D51a” notation in the top right as Hashiguchi filed in the EP ‘466 Opposition (Ex. 2025).

		(Ex. 2026)	
		U.S. App. No. 18/275,777 (Ex. 2027)	Petitioner
		U.S. App. No. 18/953,525 (Ex. 2028)	Petitioner

Moreover, as part of the Opposition in EP '466, PO filed a reference to Tokunaga bearing a handwritten annotation "Reference (7) – Appendix B" in the upper right-hand corner. Ex. 2029. Notably, Petitioner filed the *exact same* document with the same handwritten annotation as part of the prosecution history for U.S. Patent Application Nos. 17/650,803 (Ex. 2030); 18/275,777 (Ex. 2031); and 18/953,525 (Ex. 2032).

Additionally, the Notice of Opposition to EP '466, dated November 5, 2020, relied upon D19: an unpublished document with no attribution that described experiments comparing the activity of *Limulus* Factor C in two HEK293 cell lines. Ex. 2005 at 1, 4; Ex. 2033. Petitioner later submitted figures and data from D19 to the PTO in Petitioner's U.S. Patent Application Number 17/650,803, filed February 11, 2022, and published as U.S. Patent Application Pub. No. US 2023/0258647 (Ex. 2034). *Compare* Ex. 2033 Figs. 1-4 *with* Ex. 2034 Figs. 11-13, 15.

Collectively, this evidence strongly indicates that Petitioner filed the Opposition in EP '670 and thus sponsored Dr. Frohman's declaration. If so, Petitioner's positions in the EP '670 Opposition contradict what it asserts in its Petition, and the Director should view its arguments here with extreme skepticism, if not disregard them entirely.⁹ This further favors discretionary denial.

IV. CONCLUSION

In sum, Petitioner's decision to present substantially the same arguments as already considered by the PTO strongly favors discretionary denial under Section 325(d). Petitioner's election to wait years after Claim 21 issued to file its Petition and then to challenge only one out of twenty-one claims with a heavily expert-driven analysis further pushes the scale towards the Director discretionarily denying institution. As such, Patent Owner respectfully requests that the Director deny institution and maintain the patentability of Claim 21 of the '318 Patent.

Respectfully Submitted,

Dated: May 9, 2025

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

⁹ This would also amount to a violation of at least the routine-discovery obligations of 37 C.F.R. § 42.51(b)(1)(iii).

CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the above, Patent Owner's Discretionary Denial Brief, complies with the applicable type-volume limitations of 37 C.F.R. § 42.24(b). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Brief, including footnotes contains 6,053 words, as counted by the word count function of Microsoft Word. This is less than the limit of 14,000 words as specified by 37 C.F.R. § 42.24.

Respectfully Submitted,

Dated: May 9, 2025

/Alexander B. Stein/
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), lead counsel for Patent Owner hereby certifies that on May 9, 2025, a copy of this PATENT OWNER'S DISCRETIONARY DENIAL BRIEF was served via the email correspondence address of record for Petitioner's counsel of record:

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