

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

DECLARATION OF TINA MORRIS, PH.D.

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I, Tina Morris, declare:

1. I have been retained by counsel for Seikagaku (“Patent Owner” or “SKK”) to provide expert testimony in the above captioned Patent Trial and Appeal Board proceeding brought by Charles River Laboratories, Inc. (“Petitioner” or “CRL”). I am being compensated for my time on this matter at my standard rate, and my compensation does not depend on the outcome of this proceeding.

2. I understand that Petitioner has asserted that claim 21 of U.S. Patent No. 11,236,318 (“the ’318 Patent”) (Ex. 1001) would have been obvious and further understand that the Patent Trial and Appeal Board (“Board”) has instituted *inter partes* review of claim 21 of the ’318 Patent based on two grounds of unpatentability. Specifically, I understand that Petitioner has argued claim 21 of the ’318 Patent is entitled, at best, to an April 30, 2019 priority date such that the references Petitioner relies on in its Grounds 1 and 2 qualify as prior art.

3. As I discuss below, I have not been asked to comment on the priority date of claim 21 of the ’318 Patent. I have been asked to assess, assuming that claim 21 of the ’318 Patent is only entitled to an April 30, 2019 priority date, such that the references cited in Grounds 1 and 2 are prior art, whether unexpected results exist for the claimed invention.

I. EDUCATION AND QUALIFICATIONS

4. I have over 30 years of experience in protein biochemistry, structure/function analysis and characterization, covering a wide variety of proteins and expression systems. I have over 15 years of experience in compendial standardization and have specifically worked on the endotoxin assays and reference standards during my tenure at the US Pharmacopeia (USP), including the collaborative study for the second WHO international standard for endotoxin. I have over 30 peer-reviewed publications.

5. I have a master's degree in biology from the University of Oldenburg, Germany, completed with a thesis on DNA structural changes during electroporation.

6. I subsequently earned a Ph.D. in Molecular Virology from the University of Luebeck, Germany *summa cum laude* in 1994. My thesis work was focused on the recombinant expression and characterization of Hepatitis A Virus (HAV) Proteinase 3C, a self-cleaving zymogen. I expressed the serine protease in *E. Coli* and characterized the purified enzyme in comparison to other enzymes from the same virus family in terms of specificity and enzyme kinetics using an in vitro translation system.

7. I continued to work on the HAV protease during my postdoctoral work at the National Institutes of Health in Bethesda with a scholarship from the German

Cancer Research Center, in the Laboratory of Infectious Diseases with Dr. Robert Purcell. I worked on a eukaryotic expression system and the development of a viral inhibition assay for HAV in liver cells. Towards the end of my postdoctoral studies, I started studying protein-protein interactions for viral proteases using affinity mass spectrometry, a new technique at the time.

8. In 1998, I joined the protein development department at Human Genome Sciences (HGS), working on the expression and characterization of a variety of recombinant proteins for clinical development. Over the nearly six years of my tenure at HGS, my expertise focus deepened in the area of product characterization and specification development for clinical material. Endotoxin testing was routinely done on our clinical batches. Recombinant proteins from different expression systems, including Sf9, yeast, CHO and other mammalian cell lines were routinely analyzed for structure-function profiles, including glycosylation analysis. I worked on the structure function relationship, as well as molecular binding and characterization for proteins from small cytokines to large proteases and monoclonal antibodies. I worked on the product now marketed by GSK as BenLysta, a monoclonal antibody, from the pre-IND stage into Phase III.

9. I have hands-on experience in molecular cloning, PCR, sequencing, protein expression and many techniques of protein analysis.

10. In 2003, I joined the US Pharmacopeia (USP), eventually rising to Senior Vice President of Global Biologics and then Senior Vice President of Compendial Science in charge of USP General Chapters and policies. During my 15-year tenure at USP, I worked on many different biologics and biotechnology modalities. I represented USP at the WHO Expert Committee for Biological Standardization for nearly a decade and led the USP project team on the development of a replacement International Standard for Endotoxin. During that time, and in fact as part of that very study, recombinant factor C assay alternatives were starting to be considered by the regulators and actively discussed in international harmonization discussions. I have reviewed and overseen many validation and comparability studies for endotoxin data.

11. During my time at USP, I also led a team that worked on the modernization of the heparin standards for nearly six years. This included the development of a potency assay that relies on recombinant coagulation factor proteins, very similar to the recombinant factor C in this case, making me very familiar with this class of complicated proteins and the associated assay performance challenges, as well as their complicated substrates, as heparin is a glycosaminoglycan.

12. I have managed, audited, and reviewed laboratory operations and validations in a tightly regulated environment at different scales and in a global network setting.

13. After leaving the USP in 2018 as their Senior Vice President of Compendial Science, I joined the Parenteral Drug Association (PDA) as their head of Scientific and Regulatory Affairs, leading three scientific and regulatory committees, as well as their endotoxin leadership forum (ELF). The ELF at the time investigated endotoxin masking and inhibition but was also looking at the performance of different recombinant assay formats in the growing market of recombinant replacement tests, so I am very familiar with the subject matter of the case.

14. Since 2020 I have been the CEO/Executive Director of the American Association of Pharmaceutical Scientists (AAPS). In addition to overseeing the operations of the Association and working on organizational governance, I am the staff liaison to our Scientific Advisory Committee that deals with topics spanning the entire drug development trajectory.

15. A copy of my most recent curriculum vitae is provided as Exhibit 2043.

II. MATERIALS REVIEWED

16. My opinions stated herein are based on my years of education, research, and experience in the field. I have also reviewed the materials cited herein, the

Petition, the deposition transcript of Dr. Jain (Ex. 1065), as well as the following list of materials.

Exhibit Number	Description
1001	U.S. Patent No. 11,236,318
1002	Declaration of Siddhartha Jain, Ph.D., PMP
1004	Prosecution History for U.S. Application No. 16/399,386
1009	U.S. Publication No. 2015/0307864 to Mizumura
2033	D19 submitted in Opposition to European Patent No. 3441466

III. LEGAL PRINCIPLES

17. In forming my opinions stated herein, I have relied upon certain legal principles that have been explained to me by counsel. I am not an attorney and do not offer any opinions as to the law.

A. Person of Ordinary Skill in the Art

18. I understand that a person having ordinary skill in the art (“POSA”) is a hypothetical person presumed to be aware of the pertinent prior art and is a person of ordinary creativity.

19. I understand that Dr. Jain has proposed the following definition of a POSA:

Ph.D. degree in biological, chemical or biochemical engineering, molecular biology, or biochemistry and at least two years of experience in the field of 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 to a certain extent, and vice versa. This person would have been capable of understanding and applying the teachings of the '318 patent and the prior-art references discussed in this declaration.

Ex. 1002 ¶ 65.

20. I understand from counsel that PO proposes the following definition of a POSA:

Ph.D. in molecular biology, biochemistry, or enzymology and at least two years of experience with cloning genes, expressing cloned genes as proteins, and characterizing them. I understand a POSA may collaborate with others, including those with specific experience in conducting structure-function analyses of enzyme function, evaluating the activity of horseshoe crab zymogen proteins individually, or in a cascade reaction for endotoxin detection and quantitation.

21. I would have been a POSA under either parties' proposed definition as of December 2013.

B. Claim Interpretation

22. I have been informed by counsel and understand that claim terms are given their ordinary and customary meaning to a POSA, consistent with the use of

the claim term in the patent disclosure, unless the specification clearly sets forth a different definition of the term.

23. I further understand that Dr. Jain has interpreted the claim terms in claim 21 of the '318 Patent as having their plain and ordinary meaning as understood by a POSA in light of the specification and prosecution history of the '318 Patent. Ex. 1002 ¶ 71. For purposes of my analysis, I adopt the plain and ordinary meaning of the claim terms as the terms would have been understood by a POSA in light of the specification and prosecution history of the '318 Patent.

C. Obviousness

24. I understand that to assess obviousness, one looks at the following four factual inquiries: (i) the scope and content of the prior art; (ii) differences between the prior art and the claimed invention; (iii) the level of ordinary skill in the art at the time of the invention; and (iv) objective evidence or secondary considerations of non-obviousness.

25. I understand that secondary considerations of non-obviousness can include unexpected results. I understand that this analysis includes looking at whether the claimed subject matter exhibits superior properties or advantages that a person skilled in the art would have found surprising or unexpected and that any such unexpected results must be superior relative to the closest prior art.

26. I further understand that to be considered, secondary considerations of non-obviousness must have a nexus to the claimed invention.

D. Priority Date

27. I have been informed by counsel and understand that to assess whether a reference qualifies as prior art to a challenged patent claim, one must first determine the priority date (or effective filing date) of the challenged patent claim.

28. I understand that Petitioner contends claim 21 of the '318 Patent is entitled to an effective filing date no earlier than the actual filing date of the '318 Patent, which is April 30, 2019. Ex. 1002 ¶ 47. I further understand from counsel that PO disagrees with Petitioner's assessment of the priority date.

29. I do not offer any opinions as to the priority date of the '318 Patent. For purposes of my analysis only, I have adopted the April 30, 2019 priority date argued for by Petitioner and assessed, based on this priority date, whether unexpected results exist for the claimed invention. My adoption of the April 30, 2019 priority date should not be understood that I agree with Petitioner this is the correct priority date for claim 21 of the '318 Patent.

IV. OVERVIEW OF THE '318 PATENT

30. The '318 Patent was filed as U.S. Patent Application No. 16/399,386 on April 30, 2019. Ex. 1001. Claim 21 recites:

21. A horseshoe crab Factor C protein having activity of Factor C,

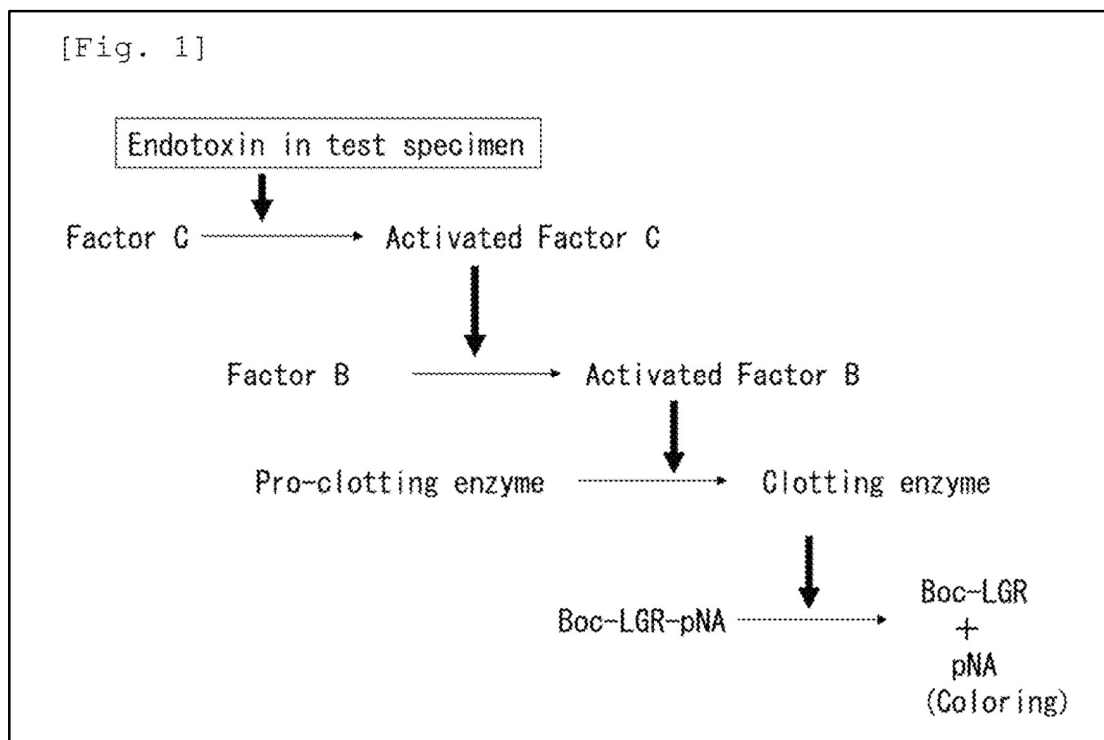
wherein the horseshoe crab is *Limulus polyphemus*, and wherein the horseshoe crab Factor C protein is produced through being recombinantly expressed from a Human Embryonic Kidney (HEK) 293 cell, and

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.

31. As the '318 Patent specification explains, “it has been known that the American horseshoe crab (*Limulus polyphemus*) undergoes a blood clotting when it is infected with a Gram-negative bacterium” such that this “phenomenon has been conventionally employed for the detection of endotoxin.” Ex. 1001 at 1:41-45. The specification continues, explaining “there is a known method for measuring endotoxin by use of a hematocyte extract of a horseshoe crab” where this “method is called a ‘limulus test,’ which employs a cascade reaction of a variety of proteins present in the lysate, which reaction occurs via contact between endotoxin and the lysate.” *Id.* at 1:46-53. Figure 1 (reproduced below) shows the cascade reaction.



Ex. 1001 at Fig. 1.

32. While the proteins in the cascade, such as Factor C, Factor B, and Pro-clotting enzyme may be obtained by capturing and bleeding horseshoe crabs, this naturally raises ecological and sustainability concerns. One way to overcome these drawbacks is to recombinantly produce the proteins. As the specification explains, while “there is known a case where Factor C, Factor B, and Pro-clotting enzyme were expressed in insect cells as host cells,” it was reported that “since the reconstituted system contains sodium chloride, magnesium sulfate, or calcium chloride in the reaction system, the cascade reaction is suppressed.” Ex. 1001 at 2:24-31.

33. Because pharmaceutical injections frequently contain a variety of salt (ions), the suppression of the cascade reaction in the presence of ions, as seen when expressing Factor C, Factor B, and Pro-clotting enzyme in insect cells as the host cells is not desirable. As such, and as the '318 Patent explains, a “[p]roblem to be [s]olved by the [i]nvention” is to ensure that the cascade reaction, including Factor C, is not susceptible to reaction inhibition in the presence of these salt (ions). Ex. 1001 at 2:63-3:8.

34. The concept of susceptibility to reaction inhibition in the presence of salt (ions) can be assessed by measuring the residual activity. Ex. 1001 at 17:20-25. The term “residual activity” is not only understood by those skilled in the art, but the '318 Patent provides an explanation of it, noting that “[t]he ‘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.” Ex. 1001 at 18:8-15.

35. The specification includes an example measuring the inhibition of activity in the presence of various salt (ions) with four different types of *Tachypleus tridentatus* Factor C compared to each other: (i) factor C expressed in Sf9 cells; (ii)

factor C expressed in CHO DG44 cells; (iii) factor C expressed in HEK293 cells; and (iv) native Factor C (TAL). Ex. 1001 at Fig. 7, 34:39-35:43.

36. As the specification explains “[w]hen a typical injection was employed as a measurement specimen, reaction with endotoxin was inhibited, as compared with the case in which injection water was used.” Ex. 1001 at 35:26-29. “The degree of inhibition varied in accordance with the type of injection and the type of host for expressing Factor C.” *Id.* at 35:29-31, Fig. 7.

A. Prosecution History of the ’318 Patent

37. During prosecution of the ’318 Patent, claim 21 was added as a new claim on August 24, 2021 as part of PO’s amendments and arguments. Ex. 1004 at 73 (claim 24). As part of this submission, PO included an affidavit from one of the inventors of the ’318 Patent, Dr. Hikaru Mizumura, as well as arguments as to why the claims, including new claim 24, should be allowed. *Id.* at 82-87.

38. In his affidavit, Dr. Mizumura explained that experimental data shows that *Limulus polyphemus* Factor C recombinantly produced using CHO cells has superior salt tolerance compared to native *Limulus polyphemus* Factor C (“LAL”) and Factor C recombinantly produced by using Sf9 as the host cells. Ex. 1004 at 84-85. Dr. Mizumura further explained that a document titled “Inhibition data” cited on the February 3, 2021 IDS (Ex. 2033) also showed that *Limulus polyphemus* Factor C recombinantly produced in HEK293 cells had superior salt tolerance as compared

to native *Limulus polyphemus* and Factor C recombinantly produced in Sf9 cells. Ex. 1004 at 85-86. Dr. Mizumura further noted that this superior salt tolerance in HEK293 cells existed regardless of the presence of (α -2,3)-linked terminal sialic acid, at least for *Limulus polyphemus* Factor C recombinantly produced in HEK293 cells. *Id.* at 86.

39. Following this submission of arguments and claim amendments, including now issued claim 21, the Patent Office allowed the claims, noting “applicant has met the burden of establishing an unexpected result.” Ex. 1004 at 21-22.

V. OBJECTIVE EVIDENCE OF UNEXPECTED RESULTS SUPPORTS THE NON-OBVIOUSNESS OF CLAIM 21

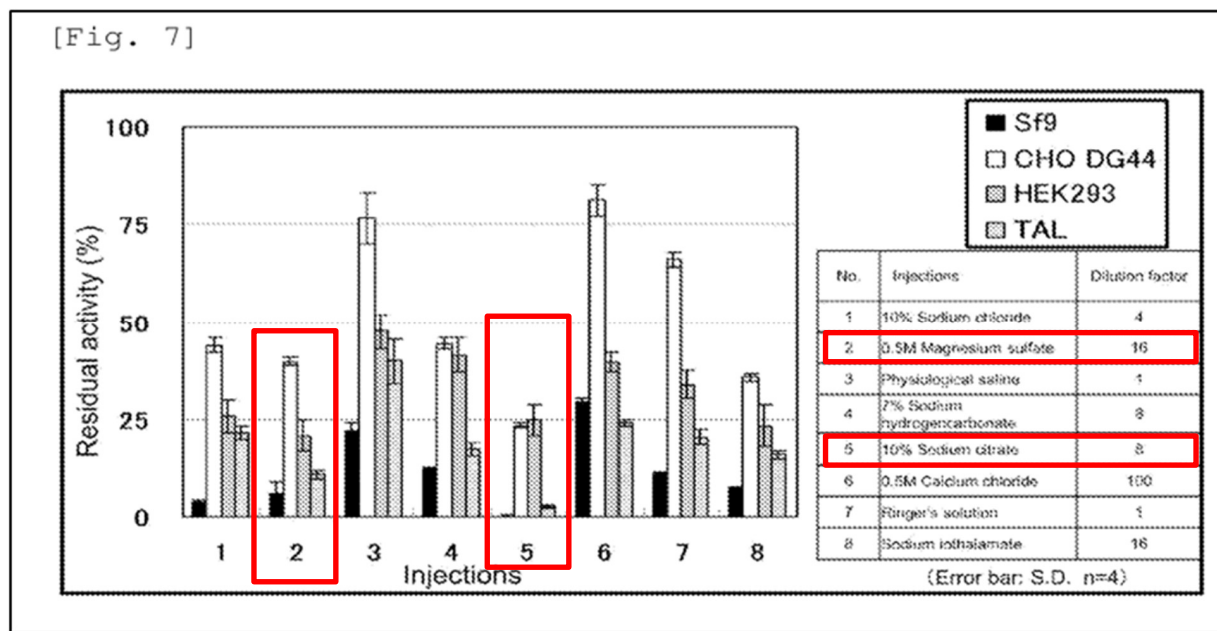
40. I understand that evidence of unexpected results can support a showing of non-obviousness. I understand that Dr. Jain disagrees that unexpected results exist. Ex. 1002 ¶¶ 193-206. In my opinion, recombinant Factor C from *Limulus polyphemus* expressed in HEK293 cells exhibits superior salt tolerance as compared to the closest prior art and thus unexpected results exist to support a finding that the claims are non-obvious.

41. As I noted above, my understanding is that Petitioner argues that the priority date of the '318 Patent is April 30, 2019 such that the references it relies on in Grounds 1 and 2 qualify as prior art. As I further noted, while I understand that PO disagrees with this assertion and asserts a priority date in December 2013, I am

not offering an opinion as to the priority date of claim 21 of the '318 Patent. My analysis and opinions are being provided assuming that an April 30, 2019 priority date is adopted such that the references in Grounds 1 and 2 qualify as prior art. I understand that if PO is successful in demonstrating that the priority date is in December 2013, then none of the references cited in Grounds 1 and 2 qualify as prior art, and Petitioner's arguments would fail for that reason alone such that I have not been asked, nor do I offer, an unexpected results opinion based on a December 2013 priority date.

42. With this assumption and understanding, I assessed whether unexpected results exist as compared to the closest prior art in April 2019. Based on Dr. Jain's invalidity grounds 1 and 2, the closest prior art reference identified is U.S. Publication No. 2015/0307864 to Mizumura ("Mizumura") (Ex. 1009), which is the United States publication of an earlier priority application to the '318 Patent and thus has an identical disclosure to the '318 Patent. Ex. 1002 ¶ 148. As described below, while Mizumura provides residual activity data in various salt solutions for *Tachypleus tridentatus* Factor C, it does not provide express residual activity data for the claimed *Limulus polyphemus* Factor C. Mizumura does though provide residual activity data for Factor C recombinantly produced in the claimed HEK293 cells and in the claimed 16 mM magnesium sulfate and 21 mM sodium citrate solutions.

43. Figure 7 of Mizumura provides residual activity ranges in various salt solutions for *Tachypleus tridentatus* Factor C recombinantly produced in different cells, including in (i) Sf9 cells, (ii) CHO DG44 cells, and (iii) HEK293 cells, as well as the residual activity of native *Tachypleus tridentatus* Factor C (TAL). Ex. 1009 at Fig. 7. As highlighted below, two of the tested salt solutions match those claimed: 16 mM magnesium sulfate (column 2) and 21 mM sodium citrate (column 5).



Ex. 1009 at Fig. 7 (annotations added)

44. From the data in Figure 7, the residual activity in the claimed salt solutions for *Tachypleus tridentatus* Factor C recombinantly produced in the two mammalian cell types (CHO DG44 and HEK293) is as follows:

- 16 mM magnesium sulfate:
 - Approximately 40% in CHO DG44 cells

- Approximately 20-25% in HEK293 cells
- 21 mM sodium citrate:
 - Approximately 25% in CHO DG44 cells
 - Approximately 20-30% in HEK293 cells

45. Claim 21 specifically requires the Factor C be from *Limulus polyphemus*, not *Tachypleus tridentatus*. To assess whether the claimed invention (*i.e.*, *Limulus polyphemus* Factor C recombinantly produced in HEK293 cells) exhibited superior salt tolerance in the claimed salt solutions as compared to the closest prior art (*i.e.*, recombinantly produced *Tachypleus tridentatus* Factor C), I reviewed data presented during prosecution of the '318 Patent showing the residual activity for recombinantly produced *Limulus polyphemus* Factor C produced not only in CHO cells, but also in the claimed HEK293 cells, and compared it to the above-described closest prior art.

46. First, I looked at the below figure submitted with the declaration of Dr. Mizumura during prosecution. As seen in the figure, the residual activity of *Limulus polyphemus* Factor C recombinantly produced in Sf9 cells, CHO DG44 cells, and CHO-S cells was assessed in various salt solutions, along with the residual activity of native *Limulus polyphemus* Factor C in those salt solutions. These salt solutions included the claimed 16 mM magnesium sulfate (column 2) and 21 mM sodium citrate (column 5).

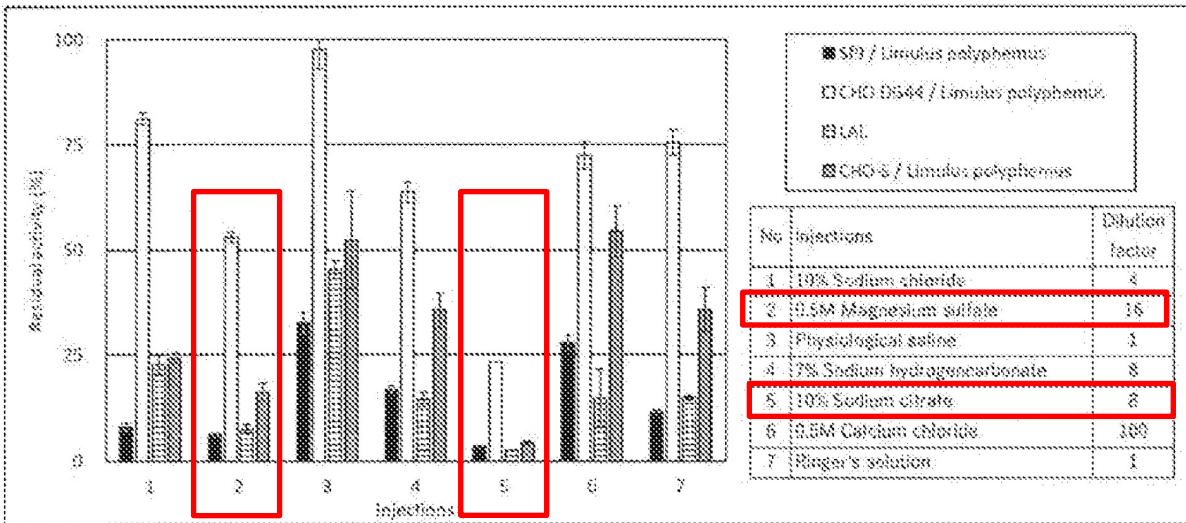


Fig. 1. Residual Activity of *L. polyphemus* Factor Cs in the Presence of Salt

Ex. 1004 at 85 (annotated).

47. From the data in Figure 1 above, the residual activity in the claimed salt solutions for *Limulus polyphemus* Factor C recombinantly produced in the mammalian CHO DG44 cell is as follows:

- Approximately 50-55% in 16 mM magnesium sulfate
- Just under 25% in 21 mM sodium citrate

48. Comparing the residual activity of *Limulus polyphemus* in CHO DG44 cells (Ex. 1004 at 85) to the residual activity of *Tachypleus tridentatus* in CHO DG44 cells (Ex. 1009 at Fig. 7), the residual activity in 16 mM magnesium sulfate is unexpectedly superior for *Limulus polyphemus* Factor C (~50-55%) as compared to *Tachypleus tridentatus* (~40%).

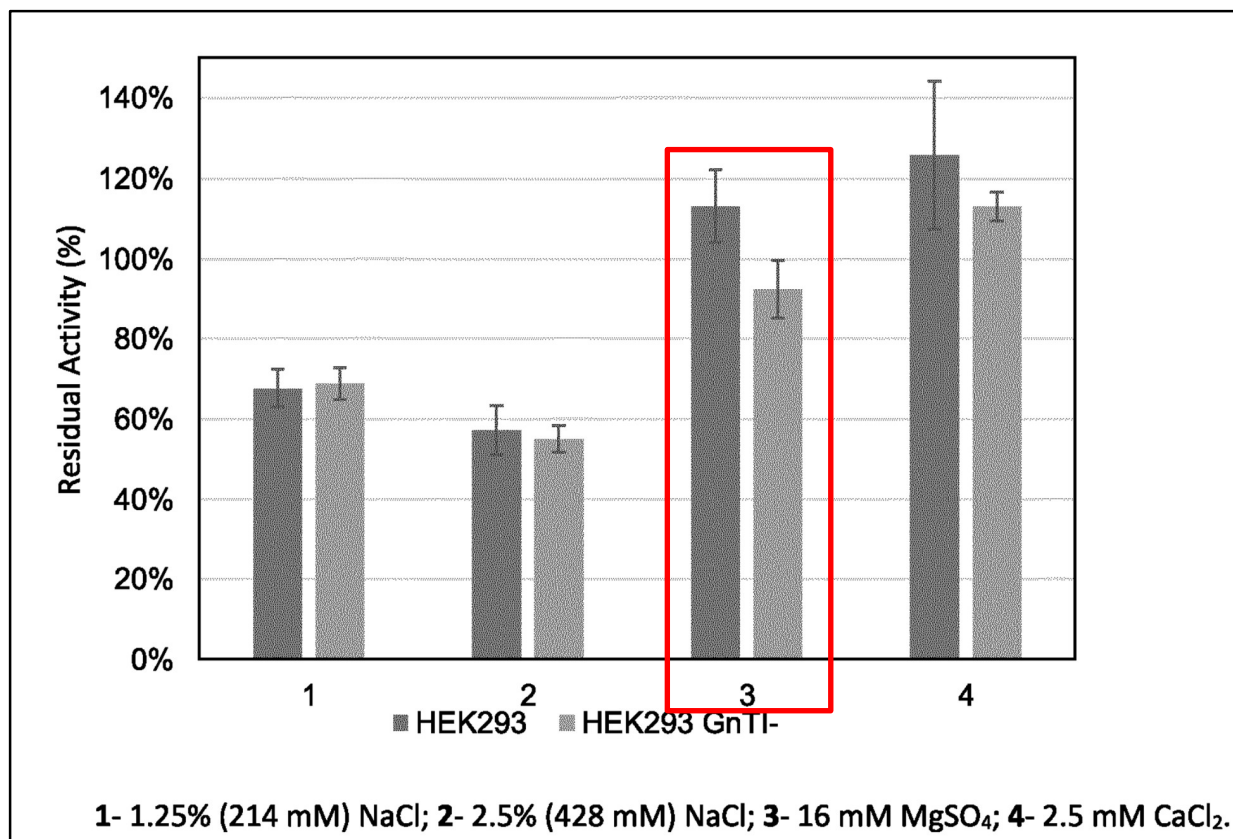
49. In published and documented history of international ring studies that include lysates derived from both *Limulus polyphemus* (LAL) and *Tachypleus*

tridentatus (TAL), the species have been consistently considered functionally equivalent in terms of activity. *See, e.g.*, Ex. 1022 at 153 (stating “[t]hese findings also lead to the idea that the hemocytes of *L. polyphemus* probably contain a coagulation system similar to that established for the *T. tridentatus* hemocytes.”). The WHO report on the 3rd International Standard for Endotoxin concluded for a study where a mixture of the 35 participating global laboratories used lysates from three different regional species that “[a]n analysis of variance of the pooled set of ln-transformed potencies (4 samples times 52 determinations) showed no significant difference between samples ($P=0.06$) or the 2 methods ($P=0.30$). It was therefore considered justified to calculate the mean potency per sample/preparation based on the pooled set of 52 results per sample.” Ex. 2107 at 7.

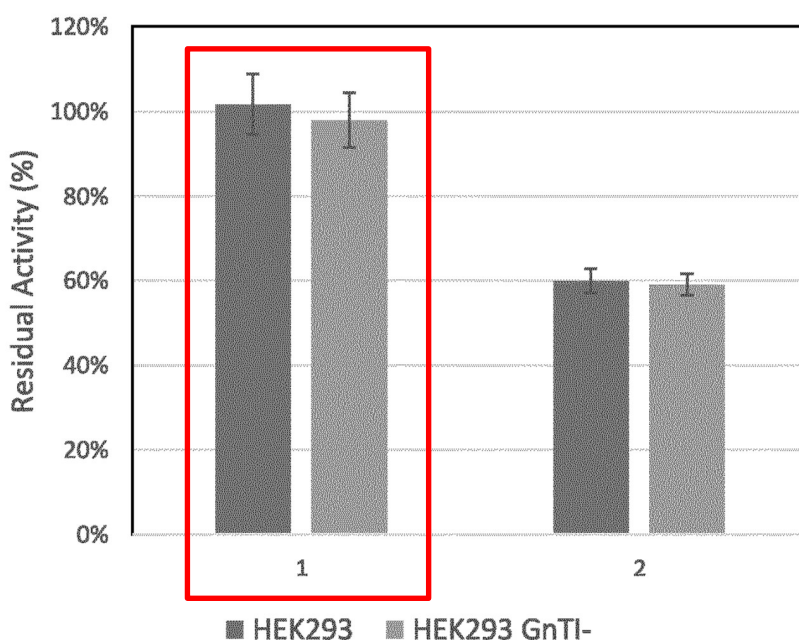
50. A POSA would have expected this equivalence to carry forward into the recombinant expression systems and not find one species being unexpectedly superior over the other. *See, e.g.*, Ex. 2062.

51. Based on this data, a POSA would have recognized that recombinantly producing Factor C from *Limulus polyphemus* exhibits unexpectedly superior results in the claimed 16 mM magnesium sulfate solution as compared to the closest prior art of *Tachypleus tridentatus* Factor C in the same claimed 16 mM magnesium sulfate solution.

52. I next looked at additional data submitted during prosecution titled “Inhibition data” with a “D19” marking at the top left of the first page (hereinafter, “D19”). Ex. 2033. This data further confirms my opinion that the claimed invention demonstrates unexpected and superior properties to the closest prior art. As explained in D19, *Limulus polyphemus* Factor C was expressed in two different host cell lines derived from HEK293 cells: (i) the HEK293 cell line that produces proteins fully glycosylated with terminal sialic acid and (ii) the HEK293 GnT1- cell line that lacks the N-acetylglucosaminyltransferase necessary to form terminally sialylated of N-glycan branches. Ex. 2033 at 1. Residual activity was measured with Factor C recombinantly produced in both cell lines in the presence of various salt solutions, including the claimed 16 mM magnesium sulfate and claimed 21 mM sodium citrate. *Id.* at 3-5, Figs. 4, 6. I have reproduced Figures 4 and 6 below.



Ex. 2033 at Fig. 4 (annotations added)



1- 21 mM sodium citrate; 2- 52 mM sodium hydrogen carbonate.

Figure 6 Residual activity (endotoxin recovery) of endotoxin in salt solutions. (n = 2)
Spiked endotoxin: 0.05 EU/mL. rLALs using HEK293 and GnTI- rFCs were used.

Ex. 2033 at Fig. 6 (annotations added)

53. As seen in Figures 4 and 6, *Limulus polyphemus* Factor C recombinantly produced in HEK293 cells exhibited residual activity between 90-120% (inclusive of error bars) in the claimed 16 mM magnesium sulfate salt solution (Fig. 4) and approximately 90-110% (inclusive of error bars) residual activity in the claimed 21 mM sodium citrate solution (Fig. 6).

54. Comparing this data in D19 to the data observed in Figure 7 of Mizumura further demonstrates that the claimed invention provides superior residual activity and thus demonstrates unexpected results. *Limulus polyphemus*

recombinantly produced in HEK293 cells exhibited residual activity between 90-120% (inclusive of error bars) in 16 mM magnesium sulfate (Fig. 4) and approximately 90-110% (inclusive of error bars) residual activity in 21 mM sodium citrate (Fig. 6). This is far superior to the residual activity observed for *Tachypleus tridentatus* Factor C recombinantly produced in HEK293 cells, which demonstrated approximately 20-25% residual activity in 16 mM magnesium sulfate (Mizumura Fig. 7, column 2) and about 20-30% residual activity in 21 mM sodium citrate (Mizumura Fig. 7, column 5).

55. As such, the claimed invention of Factor C from *Limulus polyphemus* recombinantly produced in HEK293 cells exhibits unexpectedly superior residual activity values in the claimed salt solutions as compared to the closest prior art of Mizumura and thus supports a finding that claim 21 of the '318 Patent is not obvious.

I declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: 01 Dec 2025

Tina S. Morris, Ph.D.

Tina Morris, Ph.D.