

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

SECOND DECLARATION OF BRIAN C. SCHAEFER, PH.D.

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I, Brian C. Schaefer, declare:

I. INTRODUCTION

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 at my standard hourly rate, and my compensation does not depend on the outcome of this proceeding.

2. My education and qualifications are presented in my first declaration (Ex. 2038), as well as my understanding of legal principles and background of the technology relevant to U.S. Patent No. 11,236,318.

3. I understand that as part of this proceeding, SKK plans to submit a Revised Contingent Motion to Amend that includes a proposed substitute claim 22. I have been asked to provide this second declaration for the limited purpose of addressing whether substitute claim 22 would be entitled to a December 10, 2013 priority date. Specifically, I have been asked to provide my opinion as to whether the disclosures in U.S. Application No. 14/650,767 (“the ’767 Application”) coupled with what was well understood in the art provides written description and enablement support for the full scope of proposed substitute claim 22.

II. PROPOSED SUBSTITUTE CLAIM 22

4. I have reproduced proposed substitute claim 22 below and understand that the underlining indicates proposed additions to the original claim 21 and double brackets indicate proposed deletions from the original claim 21.

5. Proposed substitute claim 22 states:

Claim 22. [Proposed substitute for claim 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]] a residual activity in the presence of 21 mM sodium citrate that is:

(i) higher than the residual activity in the presence of 21 mM sodium citrate of a corresponding *Limulus polyphemus* Factor C protein expressed in Sf9 as a host cell, or

(ii) higher than the residual activity in the presence of 21 mM sodium citrate of a native *Limulus polyphemus* Factor C protein,

wherein the horseshoe crab Factor C protein is not a horseshoe crab Factor C protein having less than 10% residual activity in the presence of 21 mM sodium citrate; and

(2) [[15% or higher in the presence of 16 mM magnesium sulfate]] a residual activity in the presence of 16 mM magnesium sulfate that is:

(i) higher than the residual activity in the presence of 16 mM magnesium sulfate of a corresponding *Limulus polyphemus* Factor C protein expressed in Sf9 as a host cell, or

(ii) higher than the residual activity in the presence of 16 mM magnesium sulfate of a native *Limulus polyphemus* Factor C protein,

wherein the horseshoe crab Factor C protein is not a horseshoe crab Factor C protein having less than 15% residual activity in the presence of 16 mM magnesium sulfate.

III. PROPOSED SUBSTITUTE CLAIM 22 IS ENTITLED TO ITS DECEMBER 10, 2013 EFFECTIVE FILING DATE

6. I understand that the proposed substitute claim 22 maintains the claim language of claim 21 regarding “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.”

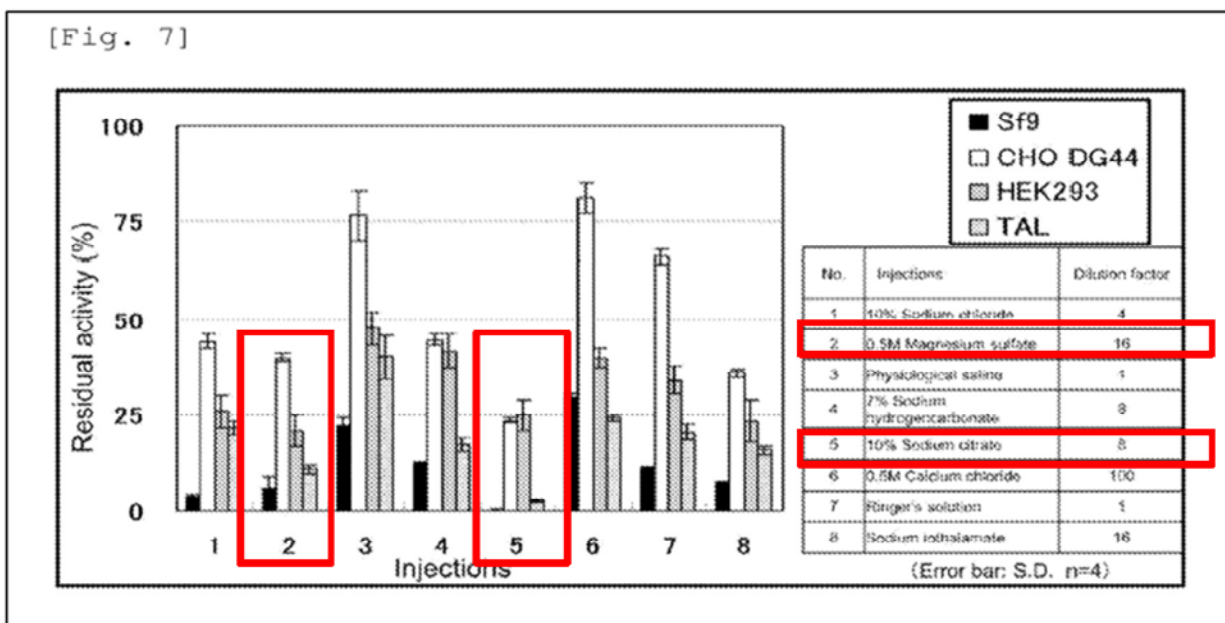
7. My original declaration (Ex. 2038) provides my opinion that Factor C from *Limulus polyphemus* recombinantly expressed in HEK293 cells has both written description and enablement support in the '767 Application. That opinion has not changed with the language in proposed substitute claim 22.

A. The '767 Application Provides Written Description Support for the New Residual Activity Language in Proposed Substitute Claim 22

8. The residual activity language in proposed substitute claim 22 has written description support in the '767 Application. Specifically, the '767 Application includes an example titled “Inhibition of activity by injection” that details measuring the residual activity of Factor C in the salt solutions, including the claimed 21 mM sodium citrate and 16 mM magnesium sulfate. EX1006 at 96-99. The '767 Application further details the procedure used for this measurement in Figure 4 and provides results in Figure 7 that show that expression of Factor C in HEK293 cells resulted in higher residual activity in the claimed salt solution as compared to (i) Factor C expressed in Sf9 cells and (ii) native Factor C. *Id.* at Fig. 7. The results also show the Factor C in HEK293 cells that had higher residual activity than Factor C in Sf9 cells and native Factor C did **not** have a residual activity less than 10% in the presence of 21 mM sodium citrate or a residual activity less than 15% in the presence of 16 mM magnesium sulfate. *Id.* at 96-99, 119, Fig. 7. The specification also explains that “[r]ecombinant Factor C (CHO) and

recombinant Factor C (HEK) showed a tendency to have low susceptibility to reaction inhibition to all the tested injections, *as compared with native Factor C (TAL)*. . . . *In contrast, recombinant Factor C (Sf9) was most susceptible* to reaction inhibition in many injections (7 injections except sample No. 6).” *Id.*

9. I have reproduced Figure 7 below with column 2 corresponding to 21 mM sodium citrate and column 5 corresponding to 16 mM magnesium sulfate:



EX1006 at 122 (annotated).

10. The '767 Application has a section titled “Modes for Carrying Out the Invention” that states the “Factor C of the present invention is a Factor C derived from a horseshoe crab” and specifically identifies *Limulus polyphemus* as a known species. EX1006 at 40. In my opinion, a POSA would have understood that the inventors considered the *Limulus polyphemus* Factor C to be a part of their invention.

11. The '767 Application also states the “present inventors have found that a recombinant horseshoe crab Factor C can be produced by use of human 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.” EX1006 at 16 [0016]. The '767 Application continues, stating the “*present invention encompasses the following modes*” and then lists a number of modes, including recombinantly produced in HEK293 cells (i) Factor C exhibiting *a residual activity of 10% or higher* in the presence of *21 mM sodium citrate*; (ii) Factor C exhibiting *a residual activity of 15% or higher* in the presence of *16 mM magnesium sulfate*; (iii) Factor C exhibiting a *higher residual activity* in the presence of 21 mM sodium citrate as *compared to Factor C expressed in Sf9 cells and/or a native Factor C*; and (iv) Factor C exhibiting a *higher residual activity* in the presence of 16 mM magnesium sulfate as *compared to Factor C expressed in Sf9 cells and/or a native Factor C*. *Id.* at 16-38 [0017].

12. In my opinion, a POSA would have understood that the inventors considered as part of their invention and described in the '767 Application: (i) Factor C from *Limulus polyphemus* recombinantly expressed in HEK293 cells having a higher residual activity in the presence of 21 mM sodium citrate than Factor C expressed in Sf9 cells or native Factor C with the residual activity of the Factor C in HEK293 cells being no less than 10%; and (ii) Factor C from *Limulus polyphemus*

recombinantly expressed in HEK293 cells having a higher residual activity in the presence of 16 mM magnesium sulfate than Factor C expressed in Sf9 cells or native Factor C with the residual activity of the Factor C in HEK293 cells being no less than 15%.

13. While I understand the data in the '767 Application is for Factor C from *Tachypleus tridentatus*, as I explain in my first declaration (Ex. 2038), Factor C proteins are highly conserved among horseshoe crab species such that a POSA would have expected residual activity in the claimed salt solutions to be highly conserved between species of horseshoe crabs. Moreover, the *T. tridentatus* and *L. polyphemus* Factor C proteins, purified from the hemolymph of the respective species, had been very well characterized biochemically via a large number of studies conducted by several different groups over a time span of decades. Collectively, these studies emphasized how Factor C proteins from these two species were functionally interchangeable. *See, e.g.*, Ex. 1022 at 150-151, 153. The revised residual activity limitations in proposed substitute claim 22 do not change my opinion as laid out in my first declaration.

B. The '767 Application Enables the New Residual Activity Language in Proposed Substitute Claim 22

14. A POSA would have also understood the '767 Application enables the full scope of proposed substitute claim 22.

15. In my opinion, proposed substitute claim 22 is narrow. It requires Factor C from a specific species of horseshoe crab (*Limulus polyphemus*) expressed in a specific cell (HEK293). The residual activity limitation in claim 22 is also narrow in that it requires specific residual activities in specifically claimed salt solutions.

16. In my opinion, undue experimentation would not have been required to make and use the claimed *Limulus polyphemus* Factor C expressed in HEK293 cells that exhibits the claimed (i) higher residual activity in the claimed salt solutions as compared to Sf9-expressed Factor C or native Factor C and (ii) residual activity being no less than the claimed 10% in 21 mM sodium citrate or 15% in 16 mM magnesium sulfate. As I discuss above, the '767 Application provides working examples showing these residual activity limitations in *Tachypleus tridentatus* Factor C, as well as how to achieve and measure these limitations. See Section III.A. Moreover, as I discuss above, the revised residual activity limitations in proposed substitute claim 22 do not change my opinion in my original declaration that a POSA would have expected the residual activity to be maintained across horseshoe crab species. *Id.*

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.

Dated: 9 April 2026



Brian C. Schaefer, Ph.D.