1 PATENT AND TRADEMARK OFFICE
2 _____
3 BEFORE THE PATENT TRIAL AND APPEAL BOARD
4 _____
5 CHARLES RIVER LABORATORIES, INC.,
6 Petitioner
7 v.
8 SEIKAGAKU CORPORATION
9 Patent Owner
10 _____
11 IPR2025-00440, PGR205-00023
12 Patent No. 11,236,318
13 Patent No. 11,959,109
14
15 DEPOSITION of SIDDHARTHA JAIN, PhD
16 Tuesday, November 4, 2025 - 9:34 a.m.
17 Wolf, Greenfield & Sacks, PC
18 600 Atlantic Avenue 23rd Floor
19 Boston, Massachusetts 02210
20
21 Reporter: Jill K. Ruggieri, RPR, RMR, FCRR, CRR
22
23
24

CRL Exhibit 1065
CRL v. Seikagaku
PG2025-00023

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1 Also present: Christine Norris

1 I N D E X
2
3 WITNESS:
4
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21 Exhibit 5 Structural studies of the 104
22 endotoxin sensing protein
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Exhibit 6	US Patent Application Publication, Pub. No.: US 2019/0241629 A1	148
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1 P R O C E E D I N G S
2
3 (Exhibit 1 marked for
4 identification.)
5 (Exhibit 2 marked for
6 identification.)
7
8 SIDDHARTHA JAIN, PhD, a witness
9 having been duly sworn, on oath deposes and
10 says as follows:
11
12 EXAMINATION
13 BY MS. LO:
14 Q Good morning.
15 Could you please state your full
16 name and address for the record.
17 A Siddhartha Jain, 773 Concord Ave,
18 Unit 406, Cambridge, Massachusetts 02138.
19 Q And it's Dr. Jain, correct?
20 A Yes. You can call me Dr. Jain, Sid,
21 Siddhartha, whatever works for you.
22 Q Okay.
23 Dr. Jain, have you ever been
24 deposed before?

1 A No, this is my first time.
2 Q Okay.
3 So do you understand that you
4 are testifying under oath today as if you were
5 testifying in court?
6 A Yes, I do.
7 Q Okay.
8 And so let me know if you don't
9 understand a question that I ask you, and I
10 will restate it.
11 Will you do that?
12 A Absolutely.
13 Q But can I assume that if you answer
14 my question, that you did understand it?
15 A Yes, and I will ask for clarification
16 if I -- if I didn't.
17 Q Thank you.
18 And do you understand that
19 you're required to answer my questions to the
20 best of your ability?
21 A I understand.
22 Q Your counsel may object to some of my
23 questions. However, unless she specifically
24 instructs you not to answer, you must answer my

1 questions.
2 Do you understand that?
3 A Okay, yes.
4 Q And for the court reporter's sake,
5 let's try not to talk over each other. So
6 please wait for the end of my question before
7 you begin your answer, and then your answer
8 should be verbal so that she can take it down
9 for the record.
10 A Understood.
11 Q Okay.
12 Is there any reason you cannot
13 testify truthfully or completely today?
14 A No, there's no reason.
15 Q If you need a break at any time,
16 please ask. All you need to do is ask --
17 answer any pending question before we take a
18 break.
19 A Understand. Okay.
20 Q And do you understand that you are
21 here to testify in connection with two
22 proceedings before the Patent Trial and Appeal
23 Board?
24 A Yes.

1 Q And one proceeding is an inter partes
2 review, or IPR, correct?
3 A Yes.
4 Q And that concerns -- and this is kind
5 of just for the record, you don't have to
6 memorize the numbers, but the IPR concerns US
7 Patent No. 11,236,318.
8 Does that sound right?
9 A That is correct, yes.
10 Q Okay.
11 And I might refer to this patent
12 as the '318 or the IPR patent today. Is that
13 okay?
14 A That is fine. I use "'318 patent" as
15 well.
16 Q Okay.
17 The other proceeding is a
18 post-grant review, or PGR, concerning US Patent
19 No. 11,959,109.
20 Does that sound right?
21 A That is right.
22 Q Okay.
23 And I might refer to that patent
24 as the '109 patent or the PGR patent.

1 Is that okay?
2 A That is fine.
3 Q And you submitted declarations
4 supporting the IPR and the PGR, correct?
5 A Yes. And in my responses, I will
6 also use similar terminology, '318 patent or
7 '109 patent, so I just want to be clear.
8 Q Perfect. Okay.
9 What did you do to prepare for
10 this deposition?
11 A I used my past experience and
12 education along with review of the
13 specifications and literature, which included
14 patents, publications, reference literature,
15 all of that, and -- and then worked on the
16 declaration with support from my -- my counsel.
17 Q What did you do to prepare for this
18 deposition today?
19 A I reviewed my declaration, reviewed
20 the literature that is referenced there in the
21 table of contents, and that was -- and then had
22 a -- some practice sessions.
23 Q So you met with your counsel?
24 A Yes.

1 Q And when did you meet with counsel to
2 prepare for the deposition?
3 A It was -- we met in person last week,
4 and then we have met from time to time kind of
5 on a weekly basis for the last couple of weeks,
6 few weeks.
7 Q In preparation for your deposition,
8 did you review any documents that you had not
9 previously considered when preparing your
10 declarations?
11 A I reviewed the additional information
12 that was listed in your -- in inventor's
13 response to my declaration, so I included those
14 documents as well in my preparation.
15 Q And you're referring to the patent
16 owner's preliminary responses?
17 A The one that came in June, yeah.
18 Q Okay.
19 So other than reviewing your
20 declaration, reviewing the references cited in
21 the declaration, the patent owner's preliminary
22 responses, and meeting with counsel, did you do
23 anything else to prepare for your deposition
24 today?

1 A No.
2 Q Approximately how much time did you
3 spend preparing for your deposition?
4 A It's hard to put a number, because
5 once you do it, it stays in your head. You're
6 always thinking. I would say probably 30, 20,
7 30 hours, 40 hours. I don't know. I've not
8 counted the hours.
9 Q But you will at some point?
10 A Yeah, I mean, for billing purpose,
11 yes.
12 Q Now, I'm going to hand you what we've
13 marked as Jain Exhibit 1. It's CRL
14 Exhibit 1002. "CRL" standing for Charles River
15 Laboratories. This is a Declaration of
16 Siddhartha Jain, PhD, submitted in the IPR.
17 MS. LOUGHRAN: Thank you.
18 Q And I'll also go ahead and hand you
19 what we've marked as Jain Exhibit 2, which is
20 the Declaration of Siddhartha Jain, PhD,
21 submitted in connection with the PGR.
22 A Okay.
23 Q And that's Exhibit 1003 in the PGR.
24 A Do I need both at the same time or

1 just to keep one for later?
2 Q You can keep both of them in front of
3 you, yeah, for now.
4 MS. LOUGHRAN: Thanks very much.
5 Q So looking at Exhibit 1, Dr. Jain, do
6 you recognize this as the declaration you
7 submitted in connection with the IPR?
8 A Yes, I do.
9 Q And that declaration addresses only
10 claim 21 of the '318 patent; is that correct?
11 A That is correct. I analyzed at first
12 claim 21 for written description and enablement
13 as of 2013, which I assessed as not being
14 described and enabled as of 2013, and at a
15 certain point in the future after 2013, I also
16 discussed in the declaration that it becomes --
17 claim 21 becomes obvious.
18 Q And looking at Exhibit 2, do you
19 recognize that as the declaration you submitted
20 in the PGR?
21 A Yes. I mean, looking at it, yes.
22 Q Okay.
23 And that PGR declaration
24 addresses claims 1 to 10 of the '109 patent; is

1 that correct?
2 A That is correct. But based on your
3 response in June, I understand that claim 10
4 was disclaimed by the inventors, which I
5 suppose leaves claims 1 to 9.
6 Q And if you look at the last page of
7 Exhibit 1 and Exhibit 2, that's your electronic
8 signature; is that right?
9 A Yes.
10 Q And you made both of these
11 declarations, Exhibits 1 and 2, under penalty
12 of perjury, correct?
13 A Yes, that is how I understood when I
14 signed.
15 Q And what is your understanding of
16 what it means to make statements under penalty
17 of perjury?
18 A What I understand is -- and I'm not a
19 lawyer, so I'm going to speak in a layman
20 term -- is that I am making statements as if
21 I'm speaking or writing under oath, so they
22 are -- I'm going to speak to the -- to the best
23 of my understanding truthfully, or write
24 truthfully. So that is how I -- I understand,

1 at a high level.
2 Q Okay.
3 And in your -- that last
4 paragraph starting "I declare that all
5 statements made," you say that "statements made
6 on information and belief are believed to be
7 true."
8 Do you see that phrase?
9 A Yes.
10 Q Now, did you make any information and
11 belief statements in your declarations?
12 A Sorry, can you repeat?
13 Q Did you make any statements that were
14 made on information and belief in your
15 declarations?
16 A All the information there is based
17 on -- or all the statements are based on the
18 information coming from, like I said, my past
19 experience and literature.
20 So I'm not sure where the
21 question is going, but all the information --
22 the statements are based on information based
23 on the literature and my experience.
24 Q Okay. Sorry.

1 So let me -- so looking at that
2 first sentence, "I declare that all statements
3 made herein of my own knowledge" -- so that's
4 one category of statements -- "are true."
5 And then there's a second
6 category of statements, "made on information
7 and belief," which you believe to be true.
8 And I was wondering, did you
9 make any statements in that second category,
10 just on information and belief, as opposed to
11 from your own personal knowledge?
12 A I would say no. If you -- if you
13 don't count my personal experience in that
14 bucket, then no.
15 Q So everything in your declarations is
16 made of your own knowledge.
17 A Yes.
18 Either, again, through
19 experience or again through reading of
20 literature.
21 Q Who drafted your declarations?
22 A I drafted with the support from my
23 counsels.
24 Q And who did the initial draft of each

1 declaration?
2 A It was -- it was a collaboration, so
3 I got a template with the legal sections filled
4 in from my counsels, along with some
5 preliminary information based on what arguments
6 I had provided to them. And then I reviewed,
7 rewrote the sections. So that's all.
8 Q Approximately how much time did you
9 spend working on your declarations?
10 A I don't recollect. It probably might
11 have been, on each of them, 15, 20 hours,
12 probably.
13 I mean, it was almost 10,
14 11 months ago. I can't recall right now how
15 many hours.
16 Q So if you turn to page 5 of
17 Exhibit 1.
18 A Yes.
19 Q There is a table that provides a list
20 of materials considered.
21 A Yes.
22 Q And there's a corresponding table in
23 Exhibit 2, the PGR declaration, as well?
24 A Yes.

1 Q So is this a complete list of the
2 materials you considered in reaching your
3 opinions for each declaration?
4 A Specific to the declaration, yes.
5 Certainly if I go back to my experience, then
6 along the period of 20, 25 years, there is more
7 literature that help build my knowledge base
8 and experience. But specifically for the
9 declaration, yes.
10 Q And that's true for both Exhibits 1
11 and Exhibit 2, right?
12 A Yes.
13 Q How did you find the references that
14 are listed in your lists of materials
15 considered?
16 A There were different ways of getting
17 the literature. Some of them were through the
18 references that were highlighted in the
19 specific -- specifications themselves.
20 Some of them were based on when
21 you start to look up the history of how all of
22 the work regarding the understanding of
23 Factor C and other proteins came along, and
24 then one reference references another paper.

1 So it's basically a sequence that way.
2 And some of the papers came
3 along from my past experience with development
4 and manufacturing of recombinant protein drugs.
5 So it came from different ways.
6 I mean, it's like -- I mean, you do a research
7 project, you start with one. That gives you
8 some references, and you look at those
9 references. They lead to more references. So
10 it's like a standard scientific investigation.
11 Q Okay.
12 Looking at the table in
13 Exhibit 1, can you identify any references that
14 you were familiar with or knew of before your
15 involvement in these matters?
16 A I know I can speak immediately the
17 Hossler one, the last one, is something I was
18 quite familiar with. That work was actually
19 done when we were colleagues, so I knew about
20 that work.
21 I was somewhat familiar with the
22 protein structure/sequence similarity paper.
23 Q Which exhibit is that?
24 A Which is 8, 1008. So those were the

1 ones I can identify immediately I was familiar
2 with even before I started to work on this
3 declaration.
4 Q Okay.
5 Then could you look at the table
6 on page 5 of Exhibit 2?
7 And were there -- in addition to
8 the Hossler paper, which is listed as
9 Exhibit 1039, were there any references that
10 you were familiar with before your involvement
11 in these matters?
12 A I had some familiarity with ExpiCHO
13 manual. I had not necessarily looked at it
14 cover to cover, but I had familiarity with
15 that.
16 Q How did your familiarity with the
17 ExpiCHO manual arise?
18 A So my work in industry has been on
19 the development and manufacturing of
20 recombinant protein drugs, and Chinese hamster
21 ovary cells are the workhorse for producing the
22 drugs. While for different drugs you end up
23 having specific processes, ExpiCHO recently
24 became a starting point for screening of

1 different components. So that is how I had the
2 familiarity about ExpiCHO system, and that's
3 why I knew about the existence of the manual.
4 Q So of the references listed in your
5 materials considered for each declaration, you
6 were familiar with the Gan paper, the Hossler
7 paper and the ExpiCHO manual.
8 Were there any other references
9 that you were previously familiar with?
10 A No, not before the declaration. I
11 mean, the concepts in some of them I was
12 familiar with, but not specifically those
13 references.
14 Q You said you conducted some
15 literature searches yourself; is that right?
16 A Yes, yes.
17 Q And what databases did you use for
18 those searches?
19 A I used PubMed. I mean, the standard
20 ones. So PubMed, Google search, Google
21 Scholar, Google Patents. And then sometimes
22 they lead you to specific journal websites,
23 like Elsevier and Wiley and all those, looking
24 deeper into those.

1 But starting point was usually
2 these aggregators like PubMed and Google
3 Scholar, Google Patents, Google general search.
4 Q Okay.
5 And do you believe that your
6 literature searches were sufficiently
7 comprehensive such that you found all of the
8 relevant information concerning the proteins at
9 issue, at least as of December 2013?
10 MS. LOUGHRAN: Objection. Form.
11 Q You can answer if you understood the
12 question.
13 MS. LOUGHRAN: Go ahead. Yes.
14 A Okay.
15 I believe it was comprehensive.
16 I don't seek to claim that I read every paper
17 in this world that was written on this topic,
18 but given that the arguments that I made were
19 supported by literature even closer to 2013, I
20 believe that I did a comprehensive search and,
21 yeah, so I don't see anything changing the
22 conclusions of my -- of my work.
23 Q Did counsel provide you with any of
24 the references listed in your materials

1 considered?
2 MS. LOUGHRAN: I'll just caution
3 the witness not to disclose the substance of
4 any discussions with counsel.
5 Q So I'm not looking for, like, a list
6 of what counsel provided you, but just a yes or
7 no, did counsel provide you with some of the
8 references listed in your materials considered?
9 A What I can say is that some of the
10 papers that were not publicly available, free
11 of cost, those I requested from the counsel,
12 and they arranged those papers for me.
13 Q I think I already asked you this, but
14 were there other materials that you considered
15 or relied on that are not listed in the tables
16 in your declarations?
17 A Yeah, you asked, and my response was
18 no other reference other than my -- the papers
19 I may have used in 20 years or 25 years of my
20 experience.
21 Q Okay.
22 So you probably recall, but in
23 your declarations, you've asserted that the
24 gene and amino acid sequences of Limulus

1 polyphemus Factor C were not known or disclosed
2 as of December 2013.
3 A That is correct.
4 Q And this assertion is important to
5 your opinions in each proceeding, right?
6 MR. KOVAR: Objection. Form.
7 Go ahead, yes.
8 A Absolutely. And this was not just an
9 opinion or assertion that I formed, but it was
10 also supported by the literature, including the
11 '498 and '629 -- '498 PCT and '629
12 specification, in which the inventors
13 themselves stated that the gene and amino acid
14 sequence for Limulus proteins, including
15 Limulus Factor C, was not known.
16 And I can read the exact text if
17 you give me those specifications.
18 And likewise, there is another
19 reference, McClymont PhD thesis. So in that
20 also, it was clearly listed that the sequence
21 for Limulus Factor C was not publicly
22 available.
23 So it's not just my assertion,
24 but it was also supported by literature that

1 came after 2013.
2 Q Did you conduct any independent
3 searching for the cDNA or amino acid sequences
4 of Factor C?
5 A I looked up on the GenBank and such,
6 UniBank and such databases, and that also did
7 not produce any Limulus sequences, including
8 Factor C, Limulus Factor C sequence.
9 Q So you searched GenBank and UniBank.
10 Any other databases?
11 A I don't recall at this point checking
12 any. These were the ones that I do recall
13 checking.
14 Q And you did those searches before
15 preparing your declarations?
16 A Yes, it was before my declaration,
17 yeah.
18 Q But those databases and your search
19 criteria aren't listed in your materials
20 considered, correct?
21 A Not in the declaration. I didn't
22 find anything. It was not...
23 Q Okay.
24 And other than searching GenBank

1 and UniBank, did you do anything else to verify
2 that the cDNA and amino acid sequences of the
3 Limulus polyphemus proteins at issue were not
4 publicly available as of December 2013?
5 MS. LOUGHRAN: Objection. Form.
6 A Can I answer?
7 Q Oh, yes, please, go ahead.
8 MS. LOUGHRAN: Yes, of course.
9 A Sorry, can you repeat your question?
10 Q So other than searching GenBank and
11 UniBank, did you do anything else to verify
12 that the cDNA and amino acid sequences of the
13 Limulus polyphemus proteins that are at issue
14 in these matters were not publicly available as
15 of December 2013?
16 MS. LOUGHRAN: Same objection.
17 A So same literature that I mentioned,
18 the databases that I said, Google, Google
19 Scholar, Google Patents, PubMed, looking for
20 all the literature that might have talked about
21 it, or even mentioned nonexistence of those
22 which -- which is how McClymont 2017 PhD thesis
23 was found during my review. And the same way
24 we have PCT '498 and '629.

1 So it was basically the same
2 sources of finding the references.
3 Q Are you familiar with a database
4 called INSDC?
5 A INSDC? No. What does it stand for?
6 Q I believe it stands for International
7 Nucleotide Sequence Database Consortium.
8 A I'm not familiar with it.
9 Q Are you familiar with a database
10 called SRA, or Sequence Read Archive?
11 A No, I'm not.
12 Q Do you know what the NCBI BioProject
13 database is?
14 A I have come across, but I have not
15 personally used it.
16 Q How have you come across the
17 BioProject database?
18 A I think it was during -- I'm speaking
19 from my memory. I may be a little bit off. I
20 think the Washington University whole genome
21 project data was recorded I think over there,
22 so that is how I came across.
23 I did see the link. I visited
24 the link, but it was after the sequence had

1 been published. I mean, the sequence was
2 published in 2014-2015, so it was just to --
3 I saw the link. It was
4 mentioned in both McClymont and '629
5 specification, so I visited after seeing those
6 links.
7 Q So the sequence that was published in
8 2014 or 2015, what sequence were you referring
9 to?
10 A So if I'm -- again, I'm recollecting
11 it accurately, then it was the whole genome
12 sequence for the Limulus polyphemus as part of
13 the in vitro -- invertebrate sequencing
14 project.
15 Q From Washington University of
16 St. Louis?
17 A From Washington University of
18 St. Louis.
19 Q Okay.
20 And were you familiar with the
21 BioProject database before your work on this
22 matter?
23 A No.
24 Q What is your understanding of the

1 information that is in the BioProject database?
2 A My understanding is that the group at
3 Washington University used next-generation
4 sequencing to sequence the whole genome of
5 Limulus polyphemus, but they did not
6 specifically identify or put together the full
7 amino acid or gene sequence for individual
8 Limulus polyphemus factors that are the subject
9 of these declarations.
10 Q You said you visited the BioProject
11 database record submitted by Washington
12 University of St. Louis.
13 Did you conduct any independent
14 searches of the BioProject database for records
15 relating to Limulus polyphemus?
16 A No, I did not.
17 Q You understand that records in the
18 BioProject database are publicly available,
19 right?
20 A As of 2015.
21 Q Or 2014?
22 A It was 2014-2015 time frame where it
23 is coming. I've seen both dates listed in
24 different documents, so that's why I'm using

1 the 2014-2015.
2 Q And do you have an opinion about the
3 public availability, which date is correct?
4 MS. LOUGHRAN: Objection. Form.
5 A I don't have any -- any opinion
6 specifically to either of the dates, but what
7 is important specific to this declaration is
8 that both of those dates are past or post
9 December 2013 and further past December 2012,
10 which is the priority date claimed for the two
11 patents.
12 Q You agree that those working in the
13 field after that genomic data was submitted to
14 BioProject, that there were tools available to
15 identify the genes for the three proteins that
16 are at issue in these matters?
17 MS. LOUGHRAN: Objection. Form.
18 A So the first thing we have to
19 understand is that the focus of this
20 declaration is to identify whether these
21 specific claims we are talking about in either
22 of them were described and enabled as of 2013.
23 So the existence of this whole
24 genome sequence in 2014 or 2015 becomes

1 immaterial from that perspective.
2 Now, if I leave that point aside
3 of 2013, and you're saying that after
4 2014-2015, when it was available, as has been
5 highlighted by the inventors themselves in the
6 '498 PCT, and if I can get a copy of that, then
7 I can just cite from there -- as well as the
8 efforts that were put in by McClymont to even
9 use that sequence to put together -- or that
10 whole genome sequence to put together the cDNA
11 sequence and amino acid sequence for Limulus
12 Factor C.
13 It's apparent that it was not
14 trivial for someone to use that genome sequence
15 as well as all the technologies to be able to
16 come up with the amino acid sequence for
17 Limulus Factor C. It required significant
18 effort to identify the sequence for Limulus
19 Factor C even after the whole genome sequence
20 was available.
21 Q And you're referring to the efforts
22 of McClymont?
23 A Yeah, because McClymont was using
24 that modality. So certainly from my reading of

1 the McClymont thesis, that is my
2 interpretation.
3 But I'm also referring in a way
4 to the statements that were made by the
5 inventors themselves, where they said how
6 difficult it was to get the sequence, and if it
7 was that straightforward, they wouldn't have
8 made that statement.
9 They did mention -- they did
10 reference this whole genome sequence project,
11 but at the same time, they were highlighting
12 the difficulty of having the full genome
13 sequence, a full DNA sequence of the Limulus
14 Factor C.
15 I'm happy to cite that if you
16 give me the reference.
17 Q We'll get to that.
18 So hypothetically, if the
19 genomic DNA of Limulus polyphemus was available
20 before December 2013, you agree that there were
21 tools available to query that sequence
22 information in order to identify the sequences
23 of Factor C, Factor B and proclotting enzyme,
24 correct?

1 MS. LOUGHRAN: Objection. Form.
2 Speculation.
3 A So let me try to understand your
4 question. You're saying if Limulus Factor C
5 sequence was available before 2013.
6 Q Oh, sorry.
7 If the Limulus polyphemus
8 genomic DNA was available prior to 2013,
9 December 2013, there were certainly tools
10 available for those working in the field to
11 identify the sequences of Factor C, Factor B
12 and proclotting enzyme within that genomic DNA,
13 correct?
14 MS. LOUGHRAN: Same objections.
15 A So it's -- it's more of a
16 speculation, or, as you said, hypothesizing.
17 Without having -- doing it myself, I can just
18 speculate. But it is -- it is possible to
19 identify -- put together the Limulus Factor C
20 sequence, just like McClymont did, if the whole
21 genome sequence was available before 2013. But
22 it would be speculation without having known
23 what a person may have done and how they may
24 have done it exactly.

1 Q Are you familiar with the NCBI
2 database, the BLAST database?
3 A Yes, yes.
4 Q And BLAST was available before
5 December 2013, correct?
6 A Yes.
7 It's -- just because a database
8 exists -- and BLAST has existed for -- for a
9 long time -- doesn't make putting together a
10 sequence or identifying a sequence to be
11 automatic, and that is what is also apparent
12 from McClymont thesis, where she did use BLAST
13 and other tools but still had to go through,
14 because they had to be put together and
15 connected to form a complete sequence.
16 So that is why I'm saying that
17 it is a possibility that a person may have been
18 able to put together, but there is -- there are
19 a number of steps that go through, and would a
20 person have been able to actually put it
21 together or not is -- is a speculation, and it
22 is -- it is a research project.
23 I mean, she did it as part of a
24 PhD thesis, so it's not like one can take the

1 sequence and do a search and say give me
2 Factor C sequence and it will come out.
3 It is a research project of its
4 own to be able to extract Limulus protein
5 sequences from the whole genome.
6 Q Have you ever used BLAST to extract
7 or identify individual genes from genomic DNA?
8 A Not personally. I mean, I've seen,
9 I've visited BLAST, but not used it for any
10 specific purpose.
11 Q Dr. Jain, I believe you mentioned in
12 your declarations that you have experience
13 using LAL, or Limulus amoebocyte lysate assays;
14 is that right?
15 A Yes, I do.
16 Q And you first use -- I'll refer to
17 that as a "LAL," L-A-L, assay?
18 A A LAL.
19 Q A LAL, okay.
20 You first used a chromogenic LAL
21 assay during your PhD studies; is that right?
22 A That is correct.
23 Q And that was sometime before 2006?
24 A Yeah. I finished in 2006. It might

1 have been somewhere around 2003 or 2004 time
2 frame.
3 Q Was that a commercially available
4 assay that you used?
5 A Yes.
6 Q And do you recall the name of that
7 assay?
8 A I don't recall. I do remember it was
9 a chromogenic, because I used it to measure
10 absorbance, but I don't recall the exact make
11 and model of the -- of the kit.
12 Q Okay.
13 Was that assay already in use in
14 your lab at the time?
15 A No, I actually introduced it. I had
16 a specific need, so I was working -- just to
17 give you context, for my PhD I was developing
18 pathogen mimetic vaccines, hydrogel-based --
19 particle-based vaccines.
20 And one of the components was to
21 attract dendritic cells, and specifically the
22 immature dendritic cells. So they should not
23 have been activated specifically by something
24 else, and endotoxin would have been a

1 contaminant to nonspecifically activate them.
2 And during my initial studies, I
3 was having challenges in getting that
4 attraction using the chemokine, and that's when
5 I realized that my particles were actually
6 contaminated because of the water source, and
7 that's when I introduced endotoxin kit to my
8 lab.
9 I tested the particles --
10 microparticles to then confirm that they are
11 free of endotoxin, and then I was able to get
12 successful outcome.
13 So that was the context of
14 introducing. It wasn't already being used. I
15 mean, I worked with -- I was the first graduate
16 student of my faculty, so there's not a lot of
17 history -- institutional knowledge that exists
18 in the lab.
19 Q That chromogenic assay used
20 recombinant Factor C?
21 A I don't recall. At that time I was
22 just using the kit as instructed in the kit.
23 Q Do you recall the species of crab
24 that was used in the kit?

1 A It was claimed to be Limulus assay.
2 I also understand that oftentimes "Limulus" is
3 used very loosely in the field. People may use
4 a different species and they still call it as
5 Limulus assay. So beyond that, I don't recall
6 what exactly the species was.
7 If it was truly a LAL assay,
8 which was certainly available, then it would be
9 Limulus.
10 Q Okay.
11 So you don't know if the
12 chromogenic assay you used was -- involved just
13 Factor C or involved the three proteins in the
14 cascade?
15 A Not during my PhD. During my time at
16 Novartis vaccines, I specifically did
17 exploration for recombinant Factor C, so at
18 that time obviously I knew that I'm using
19 recombinant Factor C.
20 Q We'll get to that.
21 A We'll get to that. I'm just saying
22 that at that point in PhD my need was to
23 purchase a kit, test my microparticles, ensure
24 that they have low endotoxin, and then be able

1 to proceed.
2 Q Did you test one sample at a time?
3 A It was -- I'm speaking from my
4 recollection of 20-something years ago. It was
5 one sample and replicates, because I was making
6 one batch of microparticles at a time.
7 Q And do you recall how long it took to
8 carry an assay out?
9 A I mean, it's very detailed
10 information from 20-plus years ago.
11 Q You can say no.
12 (Laughter.)
13 A Yeah, no, I don't recall it. It
14 wasn't too long. It might have been like
15 standard 30 minutes, but I don't exactly
16 recall.
17 Q Okay.
18 And then later you used Gel-Clot
19 and chromogenic LAL assays while at Novartis?
20 A Yes.
21 Q And what is your understanding of the
22 difference between those two types of assays?
23 A So the assays work the same, and I'm
24 not talking about recombinant, but it was the

1 PTS cartridge that was commercially available
2 for testing protein solutions, and then
3 Gel-Clot was for the vaccine formulations and
4 adjuvants that I was preparing for animal
5 studies.
6 Gel-Clot forms a gel, and the
7 readout is -- is semiquantitative. It's
8 visual.
9 On the other hand, when we are
10 doing -- using a chromogenic like PTS
11 cartridge, it's an automated system which gives
12 a quantitative readout of the value of
13 endotoxin.
14 So these are the ones that I was
15 using on a more workhorse basis until I
16 explored -- looked into recombinant Factor C.
17 Q And the assays you were using at
18 Novartis were commercially available?
19 A Yes.
20 Q And do you recall the name of the
21 company that sold them?
22 A It was Charles River.
23 Q And that was for both the Gel-Clot
24 and the chromogenic assays?

1 A Yes.
2 Q And did those assays use just
3 Factor C or the whole cascade?
4 A My understanding is they were full
5 cascade.
6 Q I think you mention in your
7 declarations that at Novartis you were
8 conducting high-throughput assays with these --
9 for endotoxins; is that right?
10 A No. So high-throughput actually came
11 in a different context. We did test -- so me
12 and my team were testing multiple samples, but
13 I would not categorize them as high-throughput
14 in any form.
15 High-throughput was in context
16 of recombinant Factor C if we wanted to expand
17 our capability.
18 Q How many samples were you testing at
19 a time?
20 A I'm speaking from my memory. Of
21 course I don't have any of the company records
22 to confirm, but typically for our animal
23 studies, we would have about ten groups, which
24 would have typically seven to nine

1 formulations, so I would say just about that
2 number of samples at a time.
3 Q So 70 to 90 samples at a time?
4 A No, seven to nine, T-O.
5 Q All right.
6 A Basically for each animal study, I
7 was preparing the formulations, then me and my
8 team were testing those formulations for
9 endotoxin and other characteristics and
10 delivering them for the animal studies, so it
11 was basically all of that set of formulations.
12 Q And you said you were evaluating
13 potentially using recombinant Factor C; is that
14 right?
15 A Yeah, it was an exploration.
16 Q And what was the result of that
17 exploration?
18 A It was a promising -- it was a
19 promising tool or kit or solution for me to
20 use. It gave comparable results to Gel-Clot
21 that I was using for my specific adjuvant
22 formulation.
23 It was chromogenic, so it did
24 have a potential for testing more samples than

1 we were able to test at a given time with
2 Gel-Clot.
3 And it confirmed the
4 non-presence of endotoxins in my adjuvant
5 formulations that I was seeing the result in
6 Gel-Clot, so it validated the result from
7 Gel-Clot.
8 Q And did your group move forward to
9 adopt the recombinant Factor C-based assay?
10 A We did not. Our intention all along
11 in general was to keep the same assays wherever
12 possible as the technical development team that
13 would take over formulations for preparing
14 clinical supplies, preclinical and clinical
15 supplies, and then do tech ops, technical
16 operations.
17 And since they did not have
18 recombinant Factor C assay in their quality
19 control labs, we shared the information but did
20 not proceed with using it as a routine method
21 for testing endotoxin.
22 Q How long did your exploratory study
23 comparing recombinant Factor C with the
24 Gel-Clot -- how long did that project last?

1 A I would say it was a few months,
2 starting from first establishing the assay,
3 testing it with well-understood samples that we
4 had for repeatability, and then testing the
5 specific sample that was giving the challenge.
6 Q Have you used or evaluated LAL assays
7 after you left Novartis?
8 A Not personally, not directly. Not
9 hands-on. But being in the biopharmaceutical
10 industry, the drugs are tested for endotoxin
11 both in process and at release. And any time
12 there was a challenge with a contamination or
13 out of -- out-of-control result in process,
14 then I would be involved in the investigation.
15 And likewise when I worked at
16 Generate:Biomedicines, I was leading process
17 development and manufacturing. So there, I was
18 again involved working with a word, CDMO.
19 These are just all capital, Contract
20 Development and Manufacturing Organization. So
21 I was working with them to set the endotoxin
22 specification.
23 So I was involved with endotoxin
24 in one form or the other, being in the

1 industry, just not hands-on.
2 Q Sure.
3 But if there was like an
4 out-of-spec result from an endotoxin assay,
5 your investigation would be into the
6 manufacturing process and the materials, not
7 the assay itself?
8 A That's not true. So I'll give you
9 one example. When we're using depth filter and
10 they have cellulosic material, and we had a
11 nonspecific -- nonspecifically higher endotoxin
12 value, because it is known that LAL reagent can
13 also be activated by beta glucan. So it can be
14 activated by beta glucans as well. And I was
15 supporting the team in resolving that
16 investigation.
17 So it's not entirely true that
18 all issues may be related to manufacturing when
19 we have issues. We also look at analytical
20 cause of a deviation.
21 Q But all of your personal and direct
22 experience using LAL assays occurred before you
23 left Novartis in January 2012?
24 A Yeah, until --

1 MS. LOUGHRAN: Objection. Form.
2 You can answer.
3 A Yes, until my time at Novartis
4 Vaccines.
5 Q You left Novartis in January of 2012,
6 approximately?
7 A That is correct.
8 Q And after that, you had no direct or
9 personal experience using LAL assays?
10 MS. LOUGHRAN: Objection. Form.
11 A I think "direct" is probably not an
12 accurate term, because if I'm supporting
13 manufacturing and supporting investigations
14 related to endotoxin, then I would consider
15 that as direct.
16 But I would say no hands-on
17 experience with the measurement of endotoxin,
18 just to be specific.
19 Q Dr. Jain, you haven't studied
20 horseshoe crab biology, right?
21 A No, other than what I read as part of
22 this declaration, not per se the horseshoe
23 biology.
24 Q Based on the references you reviewed

1 for your declarations, you would agree
2 horseshoe crabs are heavily dependent on the
3 coagulation cascade for survival, right?
4 MS. LOUGHRAN: Objection. Form.
5 A That is my understanding.
6 Q And the coagulation cascade is a
7 vital system for the survival of the crab,
8 right?
9 A That is correct. It's like their
10 protection system, like immune system.
11 Q And all four known species --
12 withdrawn.
13 All four living species of
14 horseshoe crab have the same proteins involved
15 in the cascade, a Factor B, a Factor C,
16 proclotting enzyme and coagulogen?
17 A Over a period of time of the
18 publications that were published for different
19 species, and specifically I've seen the
20 publications around Tachypleus tridentatus, or
21 TT for short, Limulus polyphemus, and some work
22 that was done on Carcinoscorpius.
23 So three out of four. I have
24 seen information, that yes, they follow the

1 same mechanism.
2 Q And the publications you just
3 referenced were all before December 2013,
4 correct?
5 A That is correct, a lot of work had
6 been done in '80s and '90s, so it...
7 Q And, Dr. Jain, you don't have any
8 experience in horseshoe crab evolution?
9 MS. LOUGHRAN: Objection. Form.
10 A Not personally.
11 Q Before your work on this matter, you
12 hadn't studied horseshoe crab evolution?
13 MS. LOUGHRAN: Objection. Form.
14 A If you are talking about horseshoe
15 evolution, then no, but you also brought in the
16 topic of the mechanism of coagulation, and the
17 answer is yes, because, like I mentioned, I had
18 a specific adjuvant, and I had invented the
19 formulation for that, and that formulation was
20 interfering with the endotoxin measurement.
21 So I was quite familiar with the
22 pathway, the coagulation pathway long before
23 2013.
24 Q Okay.

1 Do you hold yourself out as an
2 enzymologist?
3 A I don't declare myself as an
4 enzymologist; however, I have been trained on
5 the concepts of enzymology as part of my
6 education.
7 Q Do you consider yourself an expert on
8 enzymology?
9 A Not as an expert.
10 Q Do you consider yourself an expert on
11 serine proteases or serine protease zymogens?
12 A I don't consider myself as expert,
13 but I have sufficient scientific familiarity to
14 be able -- to be able to review the content for
15 this declaration for both enzymology and serine
16 proteases.
17 Q Have you ever studied differences or
18 conservation in function in proteins across
19 different species?
20 A So when we develop recombinant
21 protein drugs, it does come up in a different
22 form where we are looking at the
23 cross-reactivity between -- across species,
24 especially when we develop a drug for humans

1 but need to do animal testing in mice, in
2 monkeys or other species.
3 So in that respect, the ability
4 of -- the differences in the receptor or the
5 target across species and the ability of our
6 drug to interact with targets across species
7 does come into the picture at that time,
8 because oftentimes, we do see differences and
9 occasionally we also see non-reactivity.
10 Q Have you studied those differences at
11 a sequence level?
12 A Not personally, but I have partnered
13 with my colleagues, because when we are working
14 on selecting a candidate, drug candidate, then
15 we look at the data that is available across
16 species, in vitro and in vivo data, and I've
17 seen the data of differences in activity along
18 with explanation on why that difference may be
19 coming from at a sequence level.
20 Q Do you know what the US Pharmacopeia
21 is?
22 A Yes.
23 Q What is it?
24 A It's a nonprofit organization that

1 puts together standards around methods, around
2 drugs, around reagents, different kind of
3 things. So these are the -- they manage
4 standards within the US, same as other
5 pharmacopeias around the world.
6 Q And those other pharmacopeias around
7 the world include one for Japan and one for the
8 European Union?
9 A EP, JP, Chinese pharmacopeia.
10 Different countries have their own, or regions
11 have their own respective pharmacopeia.
12 Q And are you aware that some of those
13 chapters have been harmonized across the US,
14 Japan and EU pharmacopeias?
15 A Yes.
16 Q And specifically the chapter on
17 endotoxin testing has been harmonized across
18 those three pharmacopeias, correct?
19 A That is correct, yes.
20 Q And are you familiar with the --
21 first of all, what does "harmonization" mean in
22 that context?
23 A So harmonization, it's an initiative
24 that has been going on in different respects,

1 whether it is around methods or around
2 guidances such that the -- so specifically in
3 this case, that the same method is acceptable
4 across different regions or different
5 countries.
6 And that way, if a
7 biopharmaceutical company is manufacturing and
8 testing the drug, they do not have to test the
9 drugs against a specific -- for that specific
10 attribute, endotoxin in this case, in a
11 country-specific or region-specific manner.
12 So it basically increases the
13 interoperability across regions and countries.
14 Q And are you familiar with what goes
15 into harmonizing standards like -- in that way?
16 A Not personally, I've not been part of
17 harmonization, but I can say that from having
18 read how the ICH, for example, ICH
19 harmonization went was where representatives
20 from different regulatory bodies, they came
21 together and identified the best practices,
22 common practices, which ones were not common
23 and how they can identify the right practice,
24 where to give the flexibility, where to be more

1 prescriptive, all of that, and then put
2 together in a common document.
3 Q Sounds like a lot of work goes into
4 the harmonization process.
5 MS. LOUGHRAN: Objection. Form.
6 A Whenever you are trying to reach a
7 consensus across diverse group, it requires
8 effort.
9 MS. LOUGHRAN: Counsel, we've
10 been going for a little over an hour, so if we
11 get to a good stopping place.
12 MS. LO: Yeah, like in five
13 minutes.
14 MS. LOUGHRAN: Okay.
15 BY MS. LO:
16 Q And to your knowledge, is
17 harmonization a data-driven process?
18 A It can be dependent on many different
19 factors. Historical experience, broadly, most
20 of them data, is what I would use.
21 So based on historical
22 experience, yes.
23 Q And have you ever consulted the US
24 Pharmacopeia chapter on bacterial endotoxins

1 during the course of your career?
2 A I have referred to USP for many
3 different methods, including looking at
4 endotoxin and related to that microbial.
5 Q And when, specifically, if you
6 recall, did you consult the chapter on
7 bacterial endotoxin testing during your working
8 career?
9 A One time that just comes to my mind
10 right now, I mean, we are talking about
11 recollection, so from that, is when I was at
12 Generate:Biomedicines, and I needed to set the
13 specification for endotoxin which could cover a
14 wide range of dosage for our Phase I trial.
15 So at that time, I referenced
16 the USP compendia -- USP for endotoxin.
17 Q Have you consulted the USP chapter on
18 endotoxin testing prior to December 2013, to
19 your recollection?
20 A I likely did because of my work at
21 Novartis Vaccines, and endotoxin being a key
22 test for vaccines. But specifically when, for
23 what context, I don't recall.
24 Q Okay.

1 All right. Let's go off the
2 record.
3 MS. LOUGHRAN: Okay. Thank you.
4 (Recess.)
5 BY MS. LO:
6 Q Dr. Jain, during your undergraduate
7 studies, did you use mammalian cells for
8 recombinant protein expression?
9 A No. I had one course work on animal
10 study -- animal cell culture, but nothing
11 beyond that. I worked a lot on microbial
12 culture, so -- during my undergraduate.
13 Q During your PhD studies, did you use
14 mammalian cells for recombinant protein
15 expression?
16 A Not for protein -- recombinant
17 protein expression, but I used mammalian cells
18 for a lot of my work.
19 Q While you were at Bristol-Myers
20 Squibb, did you use mammalian cells for
21 recombinant protein expression?
22 A I did. I was working on biologics
23 drugs over there, and those biologics drugs
24 were expressed and produced using mammalian

1 cells.
2 Q What cells -- what cell lines did you
3 use?
4 A It's the Chinese hamster ovary cells.
5 Q And the biologics drugs were
6 antibodies?
7 A They were fusion proteins and
8 antibodies, monoclonal antibodies.
9 Q The fusion proteins, what were the
10 components of those?
11 A They had an Fc region and binders,
12 and both of those fusion proteins I worked with
13 were cellulated proteins, so I had direct
14 experience also with the challenges of
15 producing cellulated recombinant proteins.
16 Q How many different proteins --
17 withdrawn.
18 How many different recombinant
19 proteins did you work on while at
20 Bristol-Myers?
21 A Specifically at Bristol-Myers Squibb,
22 I worked on three drug candidates.
23 Q So at Novartis, did you use mammalian
24 cells for recombinant protein expression?

1 A So there, I did not use personally
2 for recombinant protein production, but I
3 worked with the protein biochemistry group that
4 was producing recombinant protein antigens
5 because our work was with subunit vaccines, and
6 I worked very closely with them on the
7 expression and characterization of recombinant
8 proteins.
9 Q Oh, I forgot to ask you, circling
10 back to the three drug candidates that you
11 worked on while at Bristol-Myers Squibb, do you
12 recall if those were secreted into the culture
13 supernatant or did you have to lyse the cells?
14 A Secreted.
15 Q And that's the desirable outcome,
16 right?
17 MS. LOUGHRAN: Objection. Form.
18 A Yes.
19 Q How many recombinant proteins did you
20 collaborate with the protein biochemistry group
21 at Novartis on while you were there?
22 A So I'm going to just go over the
23 different vaccines I worked on. I worked on
24 the meningitis vaccines, which had three

1 antigens, so three proteins over there.
2 And then I worked on multiple
3 candidates for RSV vaccine. I don't exactly
4 recall how many there were, but there were
5 certainly five or more candidates looked at.
6 Then -- these are the ones that immediately
7 come off top of my head.
8 Q And at Regeneron, did you use
9 mammalian cells for recombinant protein
10 expression?
11 A Yes. Again, it was all biologics
12 drugs, which are produced through recombinant
13 means.
14 Q Those biologics drugs were antibodies
15 or antibody conjugates?
16 MS. LOUGHRAN: Objection. Form.
17 A So at Regeneron, I was supporting
18 from Phase I through commercial, and there was
19 a huge diversity of modalities ranging from
20 fusion proteins to monoclonal antibodies to
21 bispecific antibody to antibody drug conjugate.
22 So it was a range of modalities that I worked
23 on.
24 And again, the fusion proteins

1 were cellulated, and I directly experienced the
2 challenges of producing consistent --
3 consistently producing cellulated proteins at
4 certain specifications.
5 Q Have you ever used insect cells to
6 express a recombinant protein?
7 A In one of my organizations, we had
8 explored using -- so let me take a step back.
9 So at Novartis Vaccines, some of
10 the -- one of the candidates for antigen was
11 initially expressed using the Sf9 cells. And
12 then at one point later on, we did explore
13 using Sf9 cells for producing another protein
14 for vaccine application.
15 Q And then did you try later --
16 withdrawn.
17 You said those proteins were
18 expressed in Sf9 cells initially. Did you try
19 to transfer that expression system to a
20 mammalian cell?
21 MS. LOUGHRAN: Objection. Form.
22 A In one of the cases I recall, we did
23 later on transfer to -- to mammalian cells. In
24 the other case, I don't believe we progressed

1 with that candidate any further based on the
2 efficacy.
3 Q Okay.
4 And the protein that was
5 transferred from Sf9 to mammalian cells for
6 expression, what protein was that? Or what
7 kind of protein was that?
8 A It was -- it was being developed as a
9 vaccine antigen.
10 Q And were those transfer efforts
11 successful?
12 A Yes.
13 Q And what mammalian cell line was the
14 expression transferred over to?
15 A As I recall, it was HEK293.
16 Q Why was HEK293 cells -- withdrawn.
17 Why were HEK293 cells selected?
18 MS. LOUGHRAN: Objection. Form.
19 A So the selection happened by the
20 vaccine development -- the R&D team that
21 preceded where I was, but part of the reason as
22 I understand was also to get a high degree of
23 cellulation -- or glycosylation, which could
24 improve the -- potentially improve the

1 effectiveness of the antigen.
2 Q Dr. Jain, have you ever isolated a
3 gene from a cDNA library?
4 A Other than a course project, not
5 otherwise.
6 Q A course project during when?
7 A During undergraduate.
8 Q Have you carried out PCRs?
9 A No.
10 Q Have you ever designed primers for
11 PCR?
12 A No, I have not.
13 Q Have you created vectors for
14 expressing recombinant proteins in a host cell?
15 A I've not created vectors. I've read
16 and reviewed information about them, but I've
17 not created vectors.
18 Q So in the course project during your
19 undergraduate studies that you just referenced,
20 what did that -- did that entail bench work?
21 A Yeah, it was -- it included lab
22 element as well, so it included DNA extraction.
23 Q Did you actually -- in the course of
24 that undergraduate project, did you actually

1 clone a gene from a cDNA library?
2 A Not from the cDNA library. It was
3 more about extracting the DNA and then -- so
4 that was basically the -- the work that I had
5 done.
6 Q Extracting DNA from what?
7 A It was from I think E. coli.
8 Q I think on your curriculum vitae it
9 says you have familiarity with enzymes.
10 Does that sound right?
11 A Which experience are you specifically
12 referring to so that I can more accurately
13 respond?
14 Q Yes.
15 MS. LO: Let's mark as
16 Exhibit 3 -- oh, I've got it here, Jain
17 Exhibit 3, this is CRL Exhibit 1003.
18 (Exhibit 3 marked for
19 identification.)
20 BY MS. LO:
21 Q So, Dr. Jain, what is Exhibit 3?
22 A Sorry. What is it?
23 Q Yes, what is it, this document?
24 A It's my CV.

1 Q Okay.
2 And this is the CV you submitted
3 in both proceedings?
4 A Declarations, yes.
5 Q So I think, directing your attention
6 to the summary, the third bullet point --
7 A Yes.
8 Q -- it starts "Experience with diverse
9 biologics modalities," and then "enzymes" is
10 listed.
11 A That's correct.
12 Q So what -- what enzymes are you
13 referencing there?
14 A So these were enzyme replacement
15 therapies that Sanofi Genzyme -- originally
16 Genzyme and then Sanofi after acquisition --
17 they were manufacturing, and I supported the
18 new process -- second-generation process
19 development and manufacturing of those enzyme
20 replacement therapies.
21 Q What kind of enzymes were involved?
22 A These are the commercial products you
23 can read about, like Cerezyme, Fabrazyme.
24 These are metabolic enzymes, usually.

1 Q Are there any updates to your CV
2 since you submitted your declaration earlier
3 this year?
4 A I'm continuing to do my consulting
5 under Shoolin Management Company, and that has
6 not changed. The clients have changed, the
7 work has -- for each client changes, but what
8 is specified here in the CV is still true.
9 Q And do you have any -- do you hold
10 any additional positions beyond the Shoolin
11 Management Company listed here currently?
12 A No. All my work that I do is done
13 under the umbrella of Shoolin Management
14 Company.
15 Q Okay.
16 Have you worked for Charles
17 River Labs before your work on this matter?
18 A For -- for Charles River? Never. I
19 mean, you can see it in my CV. I've worked for
20 biopharmaceutical companies, not the
21 diagnostics.
22 Q Oh, yes.
23 Have you worked as a consultant
24 for Charles River Laboratories before your work

1 on these matters?
2 A Never.
3 Q Dr. Jain, have you heard of a
4 technique called RACE PCR?
5 A I became aware of it through your
6 response, or inventor's response to my
7 declaration.
8 Q And that was the first time you had
9 heard of this technique?
10 A Yes.
11 Q Okay.
12 And earlier you said that you
13 had reviewed the patent owner's preliminary
14 responses. Did you also review the materials
15 cited in those responses?
16 A Yeah, I mentioned earlier that I
17 reviewed some of the -- the references within
18 the response.
19 Q Do you recall reviewing a declaration
20 by a Professor Michael Frohman?
21 A Yes, I reviewed it.
22 Q By any chance, do you have any
23 acquaintance with Professor Frohman?
24 A No. That was the first time I came

1 across his bio, his profile.
2 Q Okay. Sometimes science is a small
3 world, so I thought I would ask.
4 MS. LO: Let's go ahead and mark
5 as Exhibit 4 an excessively large document.
6 It's Seikagaku Corporation Exhibit 2004, and
7 this one was submitted for the PGR 2025-23.
8 (Exhibit 4 marked for
9 identification.)
10 BY MS. LO:
11 Q Dr. Jain, does this appear to be the
12 Frohman declaration that you reviewed recently?
13 A From the look of it, yes.
14 Q And -- withdrawn.
15 And you agree that the claims
16 that you addressed in your IPR and PGR
17 declarations require artificially expressing a
18 Limulus polyphemus Factor C protein using the
19 cDNA of that gene, correct?
20 A That is correct, specifically for the
21 IPR. For PGR, that's one of the elements,
22 because PGR specifically also has the option of
23 expressing Factor B and proclotting enzyme from
24 Limulus polyphemus in mammalian cells.

1 Proclotting is one word.
2 Q So if I can direct your attention to
3 paragraph 4 of Exhibit 4, here, Dr. Frohman is
4 describing claim 1 of EP 3 530 670, correct?
5 A Yes.
6 Q And based on his description of that
7 claim, you agree that it overlaps with the
8 claims at issue in these proceedings, correct?
9 MS. LOUGHRAN: Objection. Form.
10 A Sorry, could you repeat?
11 Q Based on Dr. Frohman's description of
12 claim 1, you agree that it overlaps with the
13 claims at issue in these PTAB proceedings,
14 correct?
15 MS. LOUGHRAN: Same objection.
16 A It has an element of it.
17 Q So when you were preparing your
18 declarations, you weren't asked to consider how
19 a skilled person wishing to obtain the coding
20 sequence of the Limulus Factor C protein would
21 have gone about obtaining that information as
22 of December of 2013, correct?
23 MS. LOUGHRAN: Objection. Form.
24 A So as of December 2013, a person

1 skilled in art did not have access to whole
2 genome sequence or any other information that
3 would have made it straightforward for them to
4 derive the full amino acid or gene sequence for
5 Limulus Factor C. And my declaration was
6 specifically focused on whether in one of them,
7 claim 21, and in the other one, claims 1 to 9,
8 they are described and enabled or not as of
9 December 2013, less so about taking up --
10 taking on a research project for coming up with
11 my own Limulus factor sequences.
12 Q You agree that the cDNA sequences of
13 T. tridentatus and C. rotundicauda Factor C
14 were known as of December 2013, correct?
15 A That is correct.
16 Q Did you analyze the sequences of
17 those proteins to determine whether they had
18 any features that would make them difficult to
19 express in mammalian cells?
20 MS. LOUGHRAN: Objection. Form.
21 A So in my experience, a sequence is --
22 Q Sorry, I'm -- I'm just asking for a
23 yes or no answer.
24 Did you analyze the sequence of

1 the known Factor C proteins for any features
2 that would make them difficult to express in
3 mammalian cells?
4 A No.
5 MS. LOUGHRAN: Objection. Form.
6 Q Thank you.
7 And then did you analyze the
8 published Limulus polyphemus Factor C sequence
9 to determine whether it has any differences
10 from the known Factor C sequences that would
11 make it more difficult to express in mammalian
12 cells?
13 MS. LOUGHRAN: Objection. Form.
14 Q Withdrawn. That was a terrible
15 question. Sorry.
16 (Laughter.)
17 Q Did you compare the Limulus
18 polyphemus Factor C sequence with the
19 T. tridentatus Factor C sequence to determine
20 if any differences would have made the Limulus
21 sequence more difficult to express in mammalian
22 cells?
23 MS. LOUGHRAN: Objection. Form.
24 A I did, and I discussed this in the

1 declaration about the differences that I had
2 identified and the similarities that existed.
3 But yes, I did do that comparison.
4 Q If you turn to paragraph 6 of
5 Exhibit 4.
6 A Second page?
7 Q Yeah. And subpart 1, Dr. Frohman
8 states that "Genomic data for Limulus
9 polyphemus was publicly available in the NCBI
10 database as of January 3, 2014."
11 Do you see that statement?
12 A Yes.
13 Q And the deposit that he's referring
14 to is from Washington University of St. Louis,
15 correct?
16 A That's correct.
17 Q Okay.
18 And do you have any basis to
19 dispute this January 3, 2014 date?
20 A No. I went and checked the entry,
21 the cover page or whatever the first page that
22 comes up using the link that was provided in
23 the '629 specification in the McClymont, and it
24 matched with what is listed.

1 Q Okay.
2 So do you have an opinion one
3 way or another whether a POSA, a person of
4 ordinary skill in the art -- well, let me start
5 over.
6 So I may use the acronym
7 "POSA" --
8 A Sure.
9 Q -- to stand for "person of ordinary
10 skill in the art."
11 Is that okay?
12 A That's fine. I'm familiar with that
13 terminology.
14 Q Okay.
15 And when I use the acronym
16 "POSA," I'll be referring to a POSA according
17 to the definitions that you've set forth in
18 your declarations; is that okay?
19 A Understood, yes.
20 Q Okay.
21 So is it your opinion that as of
22 December 2013, a POSA would not have known
23 about RACE PCR? Do you have an opinion on that
24 one way or the other?

1 A So considering I learned about the
2 RACE technique through your response, I can
3 only hypothesize or speculate on that answer.
4 And based on what Dr. Frohman has described,
5 that his first publication was I believe in
6 1988 and it has been cited a number of times, I
7 would think that a person who is doing
8 sequencing might be familiar with existence of
9 RACE technique.
10 Q Is it your opinion that as of
11 December 2013, a POSA would not have known how
12 to clone a gene out of a lambda phage cDNA
13 library?
14 MS. LOUGHRAN: Objection. Form.
15 A I would hypothesize that a person who
16 is familiar with gene sequencing might know how
17 to do the sequencing from a lambda phage.
18 Q But you don't know how to do that?
19 A No, I've not done gene sequencing.
20 Q If I can -- withdrawn.
21 If I can direct your attention
22 to paragraph 45 of Exhibit 4.
23 A Can you tell me which page is it?
24 Q It's page 10.

1 A Okay.
2 Q Do you disagree that the cDNA
3 sequence of Limulus polyphemus Factor C is very
4 similar to the other known horseshoe crabs?
5 MS. LOUGHRAN: Objection. Form.
6 A I think similarity depends on the
7 context, and in a certain context, I might say
8 yes, and in another context, I might say no.
9 I think this paragraph needs to
10 be read in context with the subsequent
11 paragraphs. But in isolation, I would say
12 there is no yes or no answer to that.
13 Q So you don't have an opinion one way
14 or the other whether the cDNA sequence of
15 Limulus polyphemus Factor C is very similar to
16 the other known species of horseshoe crabs?
17 MS. LOUGHRAN: Objection. Asked
18 and answered.
19 A I think it's not a scientifically --
20 it would not be scientifically accurate for
21 anyone to claim similarity without looking at
22 the context, because we know that cDNA codes
23 for -- will lead to a protein sequence, and
24 even one amino acid difference can change the

1 function of the protein.
2 So if you are looking at it from
3 the context of protein function, I would say
4 the answer is no. But that's not what he's
5 talking about in his declaration in
6 paragraphs 45 and 46, but that is why I'm
7 saying that I don't think any POSA would give a
8 straightforward yes or no answer, because just
9 looking at the similarity of cDNA and resulting
10 amino acid similarity would be conclusive to
11 say without knowing the context and the
12 specific level of similarity.
13 Q So you disagree with Professor
14 Frohman's statement in paragraph 45.
15 MS. LOUGHRAN: Objection. Asked
16 and answered.
17 A I don't disagree with his statement.
18 I'm disagreeing with how you're characterizing
19 the question, because when you look at 46, he's
20 talking about using that similarity to claim
21 that the protein can be expressed.
22 You asked me about general
23 similarity, and as a scientist, my answer for
24 general similarity would be I cannot comment on

1 that with a definitive answer.
2 And then -- sorry, go ahead.
3 Q Do you disagree with Professor
4 Frohman's opinion in paragraph 46?
5 A No. And if you see my declaration,
6 it's aligned with my own statement that once
7 the sequence was available in 2017-2018,
8 through the two references, a person skilled in
9 art would have a reasonable expectation of
10 being able to express using the listed
11 mammalian cells.
12 So my statement even in
13 declaration is not in conflict with his
14 statement.
15 We also have to remember that
16 this is after the sequence became known in
17 2017-2018.
18 Q So after the cDNA sequence --
19 withdrawn.
20 After you have the cDNA sequence
21 in hand, then you agree that a POSA would not
22 anticipate any difficulties expressing Limulus
23 polyphemus Factor C in mammalian cells?
24 MS. LOUGHRAN: Objection. Form.

1 A So expression of proteins in
2 mammalian cell culture, from my experience, is
3 highly complex and depends on multiple factors.
4 It's a specific protein sequence. The degree
5 of glycosylation it needs for folding the
6 specific cell line, the vector that is being
7 used, signal sequence that is being used, cell
8 culture media, cell culture conditions and all
9 that.
10 So if you ask me whether a
11 person skilled in art would not anticipate any
12 difficulties, I cannot claim that, because it
13 would only be determined once someone conducts
14 experiments.
15 What I do state in my
16 declaration is that a person would have a
17 reasonable expectation, certainly not a
18 guarantee, to be able to express Limulus
19 Factor C in CHO or HEK, H-E-K -- so CHO is
20 C-H-O -- mammalian cells.
21 Q Directing your attention to
22 paragraph 47 of Exhibit 4, do you understand
23 there's a reference to a D1?
24 Do you see that?

1 A Yes, I see a reference here.
2 Q And do you have an understanding of
3 what D1 is?
4 A Actually, I've not checked D1.
5 Q Okay.
6 On paragraph 45, Dr. Frohman
7 states that D1 discloses that Factor C from
8 other known species of horseshoe crabs have
9 been successfully expressed in Sf9, CHO DG44,
10 and HEK293 cells.
11 Do you see that statement?
12 A Yes, I do.
13 Q And that successful expression is
14 disclosed in the patents that are at issue in
15 these proceedings, correct?
16 MS. LOUGHRAN: Objection. Form.
17 A So to clarify, that would apply to
18 Tachypleus tridentatus, TT. It would not be
19 fully applicable to Carcinoscorpius, CR,
20 because the one -- Carcinoscorpius was
21 successfully expressed and secreted in Sf9
22 cells, whereas the Tachypleus, that was
23 expressed and secreted in all the three listed
24 cell lines.

1 So just to clarify that, yes,
2 it -- it would -- it -- if it is referencing
3 the specification, it's also focusing on
4 Tachypleus.
5 Q Do you understand in paragraph 47,
6 Dr. Frohman is saying he would start with the
7 cells exemplified in the disclosure of the
8 patents at issue in this proceeding, and would
9 not anticipate experiencing any difficulties in
10 expressing the Limulus polyphemus Factor C?
11 MS. LOUGHRAN: Objection. Form.
12 A So like I mentioned earlier, that I
13 have had a long history of experience working
14 with expression of recombinant protein drugs,
15 and while I agree that a POSA would start with
16 an existing procedure -- which could be the one
17 listed in D1, or could be listed in another
18 reference -- I would not claim to be able to
19 say that I would not expect -- anticipate
20 any -- experiencing any difficulties. And I
21 can certainly speak to my experiences. And if
22 you allow me to share some instances...
23 Q Maybe we can get into that a little
24 bit later.

1 A Okay.
2 Q So based on your review of his
3 declaration, Dr. Frohman is a POSA under your
4 definition, correct?
5 A Yes.
6 Q So in paragraph 47 when Dr. Frohman
7 says that he would not anticipate experiencing
8 any difficulties expressing Limulus polyphemus
9 Factor C, he is speaking from the perspective
10 of a POSA?
11 MS. LOUGHRAN: Objection. Form.
12 A So he's -- so if you look at the
13 declaration, he's -- he's making a theoretical
14 assessment. It's not like he has taken the
15 sequence and expressed it himself using one of
16 the cell lines, and he might be speaking from
17 his experience, but I have seen many
18 recombinant protein drugs that have not
19 expressed as well, even with just few amino
20 acid differences.
21 And here, we are talking about
22 as much as 10 percent difference in the
23 sequence, which is almost 100 amino acid
24 differences.

1 I've also seen situations where
2 protein can get expressed. So making a
3 definitive assessment theoretically is not
4 something that myself as a POSA would be
5 comfortable making, having seen all the
6 different experiences and challenges with
7 recombinant protein production.
8 Q So you disagree with Dr. Frohman with
9 respect to paragraph 47 of his declaration?
10 MS. LOUGHRAN: Objection. Form.
11 A At a fundamental level, I think
12 they're aligned. I believe they would be a
13 reasonable expectation. I just find it -- the
14 specific statement of not anticipating any
15 difficulties to perhaps be a little bit of a
16 more definitive and stronger statement, and
17 that part I -- it's a degree of his statement
18 which I disagree with.
19 But at a fundamental level, like
20 I said earlier -- I mentioned something
21 similar, which is aligned with his statement
22 about reasonable expectation.
23 Q So in Exhibit 2, which is your PGR
24 declaration, paragraph 107 --

1 A Just wanted to ask if we'd be taking
2 a break any time soon or --
3 Q Oh, yes, let me just ask this one
4 question, and then we can take a break.
5 THE DEPONENT: What time is it?
6 MS. LOUGHRAN: It's 11:30.
7 THE DEPONENT: Okay.
8 MS. LO: Yes. Sorry.
9 So --
10 A I'm sorry.
11 BY MS. LO:
12 Q Paragraph 107 in Exhibit 2, your PGR
13 declaration. So in this paragraph, you state
14 that, "In my experience and in the experience
15 of a POSA in the field of recombinant protein
16 production, the translatability of expression
17 process across proteins cannot be assumed."
18 Do you see that?
19 A Yes.
20 Q And that is your opinion, correct?
21 A That is what I just stated as well
22 earlier.
23 Q And you don't view that as
24 inconsistent with Professor Frohman's opinions

1 that we were just looking at?
2 A Yes, I don't see that as being
3 inconsistent. Specifically this paragraph
4 talks about the assertion that the inventors
5 made of using the same procedure that was used
6 for Factor C to express Factor B and
7 proclotting enzyme, which are quite different
8 proteins.
9 And like I mentioned, that when
10 we are -- what Dr. Frohman is talking about is
11 not expressing Factor B or proclotting enzyme.
12 All he's talking about is yes, the inventors
13 were able to express Tachypleus Factor C using
14 Sf9, CHO and HEK cells. Therefore, Limulus
15 Factor C could also be expressed.
16 And we are generally aligned,
17 because I've said that I believe a POSA would
18 have a reasonable expectation. He's just
19 saying that there would not be any difficulty.
20 So I think we are -- it would
21 not be accurate to link this statement with
22 Dr. Frohman's statement because these are two
23 different -- two different sets of proteins.
24 MS. LO: Okay. We can go off

1 the record.
2 MS. LOUGHRAN: Okay, great.
3 THE DEPONENT: Thank you.
4 (Recess.)
5 BY MS. LO:
6 Q All right, Dr. Jain. So before the
7 break, we were looking at the Frohman
8 declaration, Exhibit 4, paragraphs -- the
9 paragraphs towards the end.
10 And you understand that from
11 your review of the declaration, that
12 Dr. Frohman's opinion is that there was no
13 reason to believe that the Limulus polyphemus
14 Factor C protein would have been difficult to
15 express after the cDNA sequence had been
16 obtained, correct?
17 MS. LOUGHRAN: Objection. Form.
18 A And you're referring to paragraph 47?
19 Q Well, that subsection VIII, Roman
20 VIII.
21 A Yeah. And I shared with you my -- my
22 opinion as a person skilled in art with
23 extensive experience in producing recombinant
24 proteins, including cellulated ones, that

1 there -- why they would not be -- why there
2 would be a reasonable expectation of expressing
3 Limulus Factor C in the named mammalian cells.
4 However, it would be subject to
5 experimental verification and not a matter of
6 certainty.
7 So in that respect, I see his
8 statement to be aligned with mine, aside from
9 the degree of certainty through the choice of
10 his words.
11 Q So if I can direct your -- so you
12 don't disagree with Professor Frohman, then,
13 about difficulties -- anticipating experiencing
14 difficulties expressing the Limulus polyphemus
15 Factor C?
16 MS. LOUGHRAN: Objection. Form.
17 A It's the degree of certainty where I
18 disagree, but other than that, no.
19 MS. LOUGHRAN: Just pause so I
20 can lodge an objection, please.
21 Q Before the break, I asked you if you
22 had done a sequence comparison of the
23 polyphemus and tridentatus Factor C sequences
24 in terms of trying to identify any differences

1 that would affect the ability to express those
2 proteins in mammalian cells; do you recall
3 that?
4 A Yes, I recall your question.
5 Q And you referenced that you had done
6 that -- you answered that you had done that
7 comparison and it's discussed in your
8 declarations.
9 A That is correct.
10 Q Okay.
11 Can you identify -- well,
12 withdrawn.
13 There's no sequence alignments
14 in your declarations, correct?
15 A I believe I may have mentioned the
16 91 percent or so of sequence alignment. I
17 don't know off the top of my head.
18 Q But there's no depiction of the full
19 sequence of Factor C from tridentatus and
20 polyphemus showing the alignment in your
21 declarations?
22 A No, I did not include it.
23 Q So in your IPR declaration,
24 Exhibit 1, paragraph 82, you wrote that --

1 A Just a second. Let me get there.
2 Okay.
3 Q You're expressing an opinion that "A
4 POSA would not expect as a default that such
5 protein expression protocols would yield
6 recombinant proteins in soluble and functional
7 form from a different species of crab."
8 Do you see that statement?
9 A I see.
10 Q And the protein expression protocols
11 referenced are those that are described in the
12 '767 application?
13 A That is correct.
14 Q That's the priority application for
15 both of the patents that are actually at issue
16 in these proceedings, correct?
17 A That is correct.
18 Q And so you don't see any
19 inconsistency between this opinion in
20 paragraph 82 and Professor Frohman's opinion
21 that he would not anticipate experiencing any
22 difficulties expressing Limulus polyphemus
23 Factor C?
24 MS. LOUGHRAN: Objection to

1 form.
2 A So I think you have to look at it in
3 full context. I have said that a POSA would
4 have a reasonable expectation of expressing
5 Limulus Factor C in CHO and HEK293 cells, which
6 I see as being aligned with Dr. Frohman's
7 statement. But at the same time, I'm
8 addressing the certainty part, that a person
9 skilled in art would not and should not assume
10 by default that different proteins, different
11 sequence would necessarily express in a
12 secreted and functional state by following the
13 protocol that was successful for another
14 protein.
15 And this is simply coming from
16 the complexity, unpredictability and the
17 diversity that exists in the field of biology.
18 You can't just assume something that has been
19 done for one protein to occur likewise for
20 another protein.
21 Q What is your understanding of the
22 degree of certainty required to satisfy the
23 written description requirement?
24 A So my -- my understanding here is

1 that to meet the written description criteria,
2 the inventor should have sufficiently described
3 invention such that a person skilled in art can
4 determine that the inventors were indeed in
5 possession of the full scope of the invention.
6 Q Is it your understanding that
7 examples are required to show possession or to
8 satisfy the written description requirement?
9 A So I'm not a lawyer, but from my
10 understanding and how I've understood these
11 legal elements, while an example may not be
12 necessary in every situation, the inventor
13 needs to demonstrate that they possess the full
14 invention, in which case, in lieu of an
15 example, they would need to present a common
16 feature that would apply between what has been
17 disclosed as an example and what has not been
18 disclosed as an example for a person skilled in
19 art to conclude that yes, the inventors indeed
20 possess the full scope of the invention.
21 Q So your answer is it is your
22 understanding that examples are not required to
23 show possession?
24 MS. LOUGHRAN: Objection. Form.

1 A I think you're taking half of my
2 response, because you -- one cannot just remove
3 the example and not describe a common feature
4 either, which is the case that we have in the
5 specification here.
6 Q Is it your understanding that actual
7 possession is required to meet the written
8 description requirement?
9 MS. LOUGHRAN: Objection. Form.
10 A Again, from my understanding, being
11 not a lawyer, is that the inventors have to
12 demonstrate in some form that they possess the
13 full scope of the invention.
14 Whether they -- and if they
15 don't possess, they need to demonstrate that
16 this specific feature unequivocally will lead
17 to this aspect of the invention or this claim.
18 But it cannot be just not have an example, not
19 possess, and not have a common feature that one
20 can conclusively rely on and still have a
21 claim.
22 Q Sorry, I'm just looking for a
23 yes-or-no answer here.
24 Is it your understanding that

1 actual possession is required to meet the
2 written description requirement? Yes or no.
3 MS. LOUGHRAN: Objection. Form.
4 A The answer would be -- would be no,
5 but it comes with a specific additional
6 information that the inventors must provide.
7 It cannot be simply -- in my opinion, I don't
8 see the answer to be a yes or no, because it's
9 a contextual --
10 Q Okay.
11 A -- question and answer.
12 Q Okay.
13 Is it your understanding that a
14 specification must provide sequence information
15 to satisfy the written description requirement
16 for a biological molecule?
17 A If the sequence is publicly available
18 in prior art, then the specification -- my
19 understanding would be -- doesn't have to list
20 it as long as -- sorry, lost train of thought.
21 As long as there is an appropriate referencing
22 to the prior art.
23 Q Is it your understanding the
24 inventors should redescribe what was already

1 known in the art?
2 MS. LOUGHRAN: Objection. Form.
3 A Could you elaborate on your question?
4 Because I'm not sure what you're asking to be
5 redescribed.
6 Q Sure.
7 So you said that if the sequence
8 is publicly available in the prior art, then it
9 doesn't need to be reproduced in the
10 specification, right?
11 A Yes, that is what I said.
12 Q And there's other information that's
13 known in the art that doesn't -- that doesn't
14 need to be set forth in the specification to be
15 considered for -- in the context of written
16 description?
17 MS. LOUGHRAN: Objection. Form.
18 A If it is considered obvious by a
19 person skilled in art, or if it is referencing
20 a prior art, then yes.
21 Q And a person of ordinary skill in the
22 art is presumed to be aware of all of the
23 information in the art as of the time of the
24 invention, right?

1 A Depending on the topic, yes.
2 Q What do you mean, "depending on the
3 topic"?
4 A Depending on the topic in the sense
5 that when we look at the specification, it has
6 multiple components. It is one component of
7 expressing the recombinant protein. Another
8 component is putting together the cascade and
9 testing. The third component is demonstrating
10 residual activity, and that too in a broad
11 range.
12 So that's what I'm saying, that
13 a person skilled in art needs to have
14 familiarity either with all of those ideas or
15 it could be a group of persons skilled in art
16 who might have to be bringing their own
17 expertise into this.
18 Q In order to support a claim of
19 expressing a protein in mammalian cells
20 generally, is it your understanding that
21 inventors have to carry out that expression in
22 every known mammalian cell line in order to
23 satisfy the written description requirement?
24 MS. LOUGHRAN: Objection. Form.

1 A So you're asking me, just to clarify,
2 that for claiming expression of a certain
3 protein in a specific cell line, would the
4 inventors have to carry it out or not.
5 Q Correct.
6 A If they're claiming expression of
7 protein -- of that protein in that cell line,
8 and given the unpredictability and variability
9 that exists in biology, I would say yes.
10 Q Do you agree that mammalian cells
11 produce and secrete proteins by means of the
12 same fundamental processes?
13 MS. LOUGHRAN: Objection. Form.
14 A At a high level, yes, the mechanisms
15 of transcription, translation, post-translation
16 modification and secretion follow the same
17 biological pathway. However, the specific
18 differences between what the protein requires
19 for accurate -- for correct folding and the
20 suitability of the cell line would be on a
21 case-by-case basis.
22 And it's not just my own
23 assertion, but even if you look at the Wang
24 paper from 2002 -- W-A-N-G, Wang paper in

1 2002 -- they have extensively discussed how the
2 chaperones are important, how glycosylation is
3 important. They even mention how it's not just
4 the signal peptide that is important, but also
5 the specific amino acid sequence.
6 So even within the context of
7 this declaration, it's not just my assertion
8 based on my experience but also coming from
9 others in this field.
10 Q So in one of your prior answers, you
11 referenced a common feature. Is it your
12 understanding that the written description
13 requirement may be satisfied if there is a
14 sufficiently known correlation between the
15 disclosed function and a particular structure?
16 A Yes, if the -- the specification
17 shows a clear, unequivocal cause-and-effect
18 relationship between the common feature and the
19 invention that is being claimed.
20 Q So is it your understanding that a
21 specification needs to disclose a theory or
22 explanation for why a claimed invention will
23 work to satisfy the written description and
24 enablement requirements?

1 MS. LOUGHRAN: Objection. Form.
2 A I would expect that the specification
3 is able to demonstrate that that specific
4 common feature is able to drive that invention,
5 and that wouldn't likely be more than a single
6 experiment, but rather doing some degree of
7 scientific work to be able to demonstrate that
8 correlation between the common feature and the
9 invention.
10 Q Is it your understanding that
11 inventors have to enable more than one way of
12 obtaining the claimed invention?
13 MS. LOUGHRAN: Objection. Form.
14 A My understanding is that the
15 inventors need to enable the full scope of
16 the -- of the invention, full scope of the
17 claim.
18 So if more than one way is being
19 claimed in the invention, then yes, they would
20 need to enable all of the different ways that
21 are being claimed as part of the invention.
22 Q So I believe in your declarations you
23 reach the conclusion that the amount of
24 experiment -- well, withdrawn.

1 In the IPR specifically, you
2 concluded that the amount of experimentation
3 required to make and use the claimed Factor C
4 proteins is undue; does that sound right?
5 A That is correct.
6 Q So what amount of experimentation is
7 undue in terms of number of experiments?
8 MS. LOUGHRAN: Objection. Form.
9 A So there's not a number that one can
10 put to say X number of experiments are
11 acceptable, X plus one would be undue. And
12 that is kind of described and kind of going to
13 my -- this reminder that I'm not a lawyer, but
14 I'm referring to these Wands factors --
15 W-A-N-D-S, Wands -- that the degree of undue
16 experimentation is dependent on a multitude of
17 factors.
18 However, in this specific
19 instance of claim 21, as of 2013 to start with,
20 the Limulus Factor C sequence was not even
21 known, and not just based on my own research
22 and investigation, but also as claimed by other
23 people, like McClymont and the inventors
24 themselves, that it was not available as of

1 2013.
2 Getting that sequence itself, as
3 we have seen, and we have seen even the
4 statements from the inventors themselves in PCT
5 '498, would be a research project. On top of
6 it, then putting together the cascade, and
7 moreover, there is this broad set of residual
8 activity which goes from -- and I'm speaking
9 from memory, 15 percent to infinity from
10 magnesium sulfate, and 10 percent to infinity
11 for sodium citrate. So being able to produce
12 all of the different variations of the
13 proteins, and then confirming them against the
14 full scope of the claim, I can't see it any
15 other way but being a research project
16 requiring undue experimentation.
17 Q So is it your opinion that cloning
18 the Limulus polyphemus Factor C gene is,
19 standing alone, undue experimentation?
20 MS. LOUGHRAN: Objection. Form.
21 A It's not just my own assertion. I
22 mean, if you want, as I offered earlier, I can
23 certainly read from PCT '498 that the inventors
24 themselves mentioned that in very clear terms,

1 how difficult it was and how nobody in the
2 world had been able to get the full genome or
3 amino acid sequence, so -- and they are in the
4 trenches with these Factor C and horseshoe crab
5 proteins.
6 So I think there is a -- there
7 is a clear consistency of information, whether
8 it is from my own research or whether it is
9 from McClymont, or whether it is from the
10 inventors themselves, that not only was the
11 sequence not available, but it was not
12 straightforward or easy for a person skilled in
13 art to get the sequence of...
14 Q I -- I understand all of that, but
15 I'm just trying to get to see if it is your
16 opinion that cloning the Limulus polyphemus
17 Factor C gene, standing alone, just that, is
18 undue experimentation.
19 A Yes.
20 MS. LOUGHRAN: Objection. Form.
21 Q And is it your opinion that
22 expressing Limulus polyphemus Factor C, once
23 the sequence was known, in HEK cells, HEK293
24 cells, is undue experimentation?

1 MS. LOUGHRAN: Objection. Form.
2 A No, I mentioned that there would be a
3 reasonable expectation.
4 Q Okay.
5 So we've referenced -- sorry.
6 A I mean, if I -- if I can just
7 elaborate a little bit on the first part of
8 what you're talking about, the -- getting the
9 sequence, why would that be undue
10 experimentation, I'm happy to speak further on
11 that.
12 Q We'll maybe circle back to that.
13 A Okay.
14 Q So you referenced the McClymont
15 thesis a number of times in your answers today,
16 but you understand that Karen McClymont was not
17 a POSA under your definition, correct?
18 A I cannot specifically claim that
19 because I don't know how long she spent on her
20 PhD. And given that I've mentioned that the
21 education can substitute for experience and
22 vice versa, so from that perspective, and
23 specifically she was working on Limulus
24 Factor C, so I would consider that from the

1 perspective of elucidating the Limulus Factor C
2 sequence, for that specific part, I would -- I
3 would consider her as a person skilled in art.
4 Q Do you know what her PhD was in?
5 A It was on looking at -- I mean, I'm
6 going to verbalize in my own words, not exactly
7 the title.
8 So what she was looking for was
9 the LPS -- lipopolysaccharide binding region on
10 Limulus Factor C, and specifically Limulus
11 Factor C because the LAL reagent is the most
12 commonly used reagent for endotoxin detection.
13 So as part of that, she
14 identified the Limulus Factor C sequence based
15 on the whole genome sequence that was public at
16 that point, and then she attempted to express
17 different domains of Limulus Factor C in
18 different expression systems, eventually using
19 E. coli, and then doing structural analysis on
20 those domains.
21 Q But you don't know if she has a PhD
22 in biological, chemical or biochemical
23 engineering, molecular biology or biochemistry?
24 A Specifically, no, I don't know -- I

1 mean, she was doing a PhD. That's how she --
2 she did her work as part of her PhD.
3 Q And she was not a POSA, she didn't
4 have her PhD in December of 2013, right?
5 A She did not have her PhD as of
6 December 2013, because she got her PhD -- her
7 PhD thesis is dated in 2017.
8 Q And her thesis was not written from
9 the perspective of a POSA in 2013, correct?
10 MS. LOUGHRAN: Objection. Form.
11 A I'm not sure where you're going, but
12 her thesis was written in April 2017. So 2013
13 is not the date when the thesis was published.
14 Q And her thesis was not written from
15 the perspective of a POSA in 2017.
16 MS. LOUGHRAN: Objection. Form.
17 A I'm not sure where you're going
18 but -- I mean, she -- she did all the work on
19 Limulus Factor C, and that was relevant for
20 this declaration.
21 Q She didn't write her thesis from the
22 perspective of a POSA the way you defined it
23 for your declarations?
24 A So I think we have to take a step

1 back here on -- on the POSA.
2 When we look at creating
3 specification, the three elements I mentioned
4 earlier are being able to express the protein,
5 put together the cascade, and then measure
6 residual activity, which needs the person to
7 be -- not be doing all the gene sequencing.
8 You need the person to already
9 know that the sequence exists and they can
10 express the protein, they can characterize the
11 protein, put together the cascade and measure
12 the residual activity.
13 So the POSA definition in my
14 declaration is based on the specification --
15 specifications of '318 and '109. It is only
16 because the inventors did not possess the full
17 amino acid or gene sequence that we are having
18 all this conversation on and on about
19 somebody -- a POSA claimed to elucidate the
20 sequence themselves.
21 But that is not, in my
22 understanding, even the requirement for someone
23 to -- to be able to use the '318 specification.
24 I mean, so it's -- it's like a scope creep we

1 say -- in the industry we use this, as like we
2 have a scope and now we are going outside the
3 scope to say, oh, let's add five other things
4 into that.
5 Q So I'm going to -- if there is such a
6 thing, I'm going to move to strike that last
7 answer as nonresponsive.
8 My question was, McClymont
9 didn't write her thesis from the perspective of
10 a POSA the way you that you have defined it in
11 your declarations. And I think your answer is
12 no.
13 Is your answer no?
14 MS. LOUGHRAN: Objection. First
15 I'm going to oppose your motion. I'm also
16 going to object to the form of that question.
17 Q She didn't have your definition of a
18 POSA in mind when she was writing her thesis,
19 correct?
20 A No, she --
21 MS. LOUGHRAN: Objection.
22 Argumentative.
23 A She did not, but then my definition
24 of POSA --

1 Q Okay.
2 A -- is specific for the specification.
3 Q Thank you.
4 A And I think that is -- the definition
5 of POSA is not being expanded to something that
6 was not even in the scope of the specification.
7 Q And at the time that Karen McClymont
8 conducted the research described in her
9 dissertation, she had not yet obtained her PhD,
10 correct?
11 A That is correct.
12 Q And the McClymont thesis doesn't
13 describe measuring residual activity of
14 Factor C, correct?
15 A It does not. It is described in the
16 specification.
17 Q Okay.
18 Let's go ahead and mark the
19 McClymont thesis.
20 (Exhibit 5 marked for
21 identification.)
22 MS. LO: Exhibit 5. Thank you.
23 And this was submitted as IPR Exhibit 1010 and
24 PGR Exhibit 1011. We can mark both or just the

1 one.
2 MS. LOUGHRAN: Whatever you
3 want. Whatever is easiest for you.
4 MS. LO: Let's mark the IPR
5 Exhibit 1010.
6 BY MS. LO:
7 Q Dr. Jain, just for housekeeping, you
8 submitted the same thesis in both -- withdrawn.
9 It was the same McClymont thesis
10 attached -- referenced in your -- in your
11 declarations for both the IPR and the PGR,
12 correct?
13 A Yes, it's the same one.
14 Q Okay.
15 A I can't create the document.
16 Q Okay.
17 So -- and do you recognize
18 Exhibit 5 as Karen McClymont's PhD thesis dated
19 March 2017?
20 A Yes, I do.
21 Q If you go to page 12 on the internal
22 pagination.
23 A The author's declaration?
24 Q Yes.

1 A Okay.
2 Q So she submitted this thesis in
3 September 2016.
4 Is that what it looks like?
5 A Yes.
6 Q So the work that's described in the
7 thesis was done before September 2016, correct?
8 A Yes, that is how it happens in the
9 PhD projects.
10 Q Okay.
11 And then if we go to page 38 of
12 Exhibit 5, Section 2.3, Assembly of the Limulus
13 Polyphemus Factor C Coding Sequence.
14 Do you see that?
15 A Yes, I see 2.3.
16 Q And in this section, Ms. McClymont
17 says that she received prerelease access to the
18 Limulus polyphemus genome data generated by an
19 institute at the Washington University of
20 St. Louis?
21 A Yes, I see that statement.
22 Q And that's the same data that, if you
23 recall from Professor Frohman's declaration,
24 said it was published as of January 2014,

1 correct?
2 A That is correct.
3 Q And so Ms. McClymont presumably
4 obtained the genomic data before January 2014,
5 given her statement here?
6 MS. LOUGHRAN: Objection. Form.
7 A It appears so.
8 Q And do you have any reason to believe
9 that other scientists could not have obtained
10 the same prerelease access?
11 A It's -- it's mere speculation,
12 because one scientist or one group releasing
13 data during prerelease could be under certain
14 restrictions or for specific usages -- uses.
15 So having a generalized
16 statement would be completely speculative and
17 likely the answer would be no. It's a
18 case-by-case basis.
19 Q Do you recall from your review of the
20 McClymont thesis that Ms. McClymont engineered
21 the glycosylation sites out of her -- out of
22 the Factor C cDNA sequence that she expressed?
23 A That is correct. She specified it in
24 one of the paragraphs with specific amino acids

1 that she mutated.
2 MS. LO: Can we go off the
3 record?
4 (Discussion off the record.)
5 (Lunch recess.)
6 BY MS. LO:
7 Q Welcome back, Dr. Jain.
8 A Thank you.
9 Q Did you discuss the substance of your
10 testimony with counsel over the break?
11 A No.
12 Q If we can have Exhibit -- please turn
13 to paragraph 84 in your IPR declaration,
14 Exhibit 1.
15 A Paragraph 84?
16 Q Yes.
17 A Okay.
18 Q And in the -- kind of in the middle
19 of this paragraph, you wrote, "While a POSA in
20 2013 may have" had certain expectations. Do
21 you see that?
22 A "A POSA would have expected each
23 species," that part of --
24 Q Sorry. I can read the sentence.

1 You wrote, "While a POSA in 2013
2 may have expected the native members of these
3 varied horseshoe crab species to behave
4 similarly in terms of their hemolymph activity
5 to detect endotoxin."
6 A I see that sentence, yes.
7 Q So you used the term "may."
8 Is that because you doubt that
9 this would have been the expectations of a
10 POSA?
11 A So based on the information that was
12 available and based on my literature review,
13 there was information available for Tachypleus
14 and Limulus on the mechanism on the cascade.
15 It was also understood that
16 Carcinoscorpius behaved the same way. So that
17 would have been an expectation for a POSA in
18 2013 to know that -- that in the native
19 horseshoe crab, the hemolymph will function in
20 the same or similar manner.
21 Q Can you turn to paragraph 89 in the
22 same declaration.
23 So in this paragraph you wrote
24 that a POSA would have -- well, withdrawn.

1 In this paragraph, you wrote
2 that, "As of 2013, a POSA would have expected
3 that differences in gene or amino acid
4 sequence," and I'll omit the parenthetical,
5 "would lead to differences in protein
6 structure, and, in turn, differences in protein
7 function."
8 Do you see that?
9 A Yes.
10 Q Okay.
11 So is the converse of that true?
12 If a POSA knew that proteins function the same,
13 then they would also understand that any
14 differences in sequence or structure does not
15 affect function?
16 MS. LOUGHRAN: Objection. Form.
17 A If the -- so let me just understand.
18 So if the function is the same,
19 then the sequence or structure would be the
20 same as well? Is that what you're asking?
21 Q No.
22 So if two proteins function the
23 same, then they would -- a POSA would
24 understand that any differences in sequence or

1 structure between the two proteins does not
2 affect their overall function?
3 MS. LOUGHRAN: Objection. Form.
4 A So this is where the definition of
5 "function" becomes relevant. Between -- if you
6 look at paragraph 84, the function there I'm
7 describing is the ability to -- for the three
8 factors to come together and then -- and to
9 cleave coagulogen to form the clot. That's
10 looking at function from a macroscopic
11 perspective.
12 In paragraph 89, I'm talking
13 about the function of individual protein in
14 terms of the enzymatic activity, and that
15 subsequently extends to the concept of residual
16 activity.
17 So it comes down to how we are
18 defining the function to be able to say whether
19 the function would be the same or not between
20 the two proteins.
21 So just to put it another way,
22 if Tachypleus factors and Limulus factors are
23 all individually able to drive the coagulation
24 in respective organisms, that does not mean

1 that Tachypleus Factor C and Limulus Factor C
2 will necessarily have a similar enzymatic
3 activity or residual activity.
4 Q I think my question was more in the,
5 you know, macroscopic function sense.
6 A Okay.
7 Q So if we know that Factor C from
8 tridentatus is a serine protease zymogen, it
9 binds to LPS and then is activated as a
10 protease, and we know that Limulus polyphemus
11 Factor C functions in the same way, then
12 according to the inverse of the reasoning that
13 you've set forth in paragraph 89, then it would
14 follow that differences in sequence or
15 structure between those two proteins does not
16 affect their overall function.
17 MS. LOUGHRAN: Objection. Form.
18 A So that would be -- these
19 observations are within the same species and
20 with a specific set of proteins within the
21 cascade. So Tachypleus Factor C, with
22 Tachypleus Factor B, with Tachypleus
23 proclotting enzymes, and same with Limulus
24 factors.

1 So yes, I mean, they're working
2 on their own, but bringing them -- because
3 simply because they both are able to drive
4 coagulation, trying to say that they would have
5 similarities in some form between each other
6 would be inaccurate, because at the end of the
7 day, in nature, they're working with the
8 respective factors from their own species.
9 Q But they are, in fact, similar in --
10 in sequence, correct? 90 percent homologous?
11 MS. LOUGHRAN: Objection. Form.
12 A So let me just clarify, because I
13 keep seeing this 90 percent all along, and we
14 have to understand that 90 percent in this
15 context -- on this residual activity and all
16 that discussion is, for lack of a better word,
17 it's a meaningless representation.
18 The 90 percent number originally
19 came along in the '90s when all these databases
20 were being created for protein database, gene
21 databases, and people were trying to do the
22 matching to find similar proteins and similar
23 genes.
24 And the computational power that

1 was needed was huge, so they used 90 percent
2 criteria to kind of form the islands
3 [phonetic]. And later on, 90 percent criteria
4 was used.
5 But if I have an unknown
6 protein, a protein with an unknown function,
7 then if it is having a 90 percent -- and some
8 use 95 percent sequence similarity -- can I
9 assign a function based on the other proteins
10 with similar sequence.
11 But that function was, like, I
12 have a serine protease, another unknown protein
13 with 90 or 95 percent similar sequence, so the
14 unknown protein would likely be a serine
15 protease, or a protease.
16 So that is where 90 percent
17 comes from. And I keep seeing this whole
18 discussion about 90 percent and because it is
19 90 percent, we can assume a lot of things.
20 We already know from the field
21 of protein biology that even changing one amino
22 acid can make a significant difference in its
23 structure, like we know about hemoglobin and
24 sickle cell anemia, hemoglobin. Or it could

1 have a change in its activity, its function. A
2 lot of those kind of things can change.
3 I mean, it's -- using this whole
4 90 percent similarity or homology argument is
5 just -- I'm just putting -- sharing that it
6 just doesn't -- it's a scientifically
7 inaccurate way of looking at residual activity.
8 Q Okay.
9 But you agree that as a fact,
10 the cDNA sequences of T. tridentatus and
11 Limulus polyphemus Factor C are 90 percent
12 identical?
13 A Yes.
14 Q Okay.
15 And is it your opinion that any
16 small change in an enzyme's protein sequence
17 can result in changes to its structure, which
18 then can impact function?
19 A Yes.
20 MS. LOUGHRAN: Objection. Form.
21 Q So even if those changes in sequence
22 are not in the active site of the enzyme?
23 A Yes, because the proteins work in
24 three-dimensional state, and if a change is

1 happening that is -- that may not be at the
2 catalytic site, but could change the structure
3 of the catalytic site, that can certainly have
4 an impact on the function of the protein.
5 Q Is any of your professional
6 experience in studying the sequence and
7 structure of enzymes across species?
8 A I cannot recall at this point of any
9 specific experience. I've used enzymes for
10 different -- for my research projects and all
11 that, but I can't recall comparing across
12 species.
13 However, I can say that I have
14 been involved with looking at antibody binding
15 to targets across species, and we have clearly
16 seen differences in binding affinity to the
17 point that sometimes the antibody may not even
18 bind to a target from another species.
19 Q Antibodies aren't enzymes, though,
20 right?
21 A They're not. But at the same time,
22 enzymes are actually considered to be more
23 sensitive because they need to have much more
24 of a specificity to the -- to the substrate.

1 So a change in the catalytic
2 site, substrate binding site could render the
3 enzyme to be nonfunctional.
4 There are enzymes that exist
5 that cannot even survive staying at room
6 temperature for long period of time. One of
7 the enzymes I supported the manufacturing of,
8 we had to do processing of it under
9 refrigeration because enzymes can be very
10 sensitive.
11 Q Well, I -- we'll move on from there,
12 assuming you were done with your answer.
13 A I'm done.
14 Q Okay.
15 So if you can turn to
16 paragraph 156 in your IPR declaration. There's
17 a reference --
18 A Just give me... yes.
19 Q There's a reference you call
20 Mizumura, correct?
21 A Yes.
22 Q And that Mizumura has the identical
23 disclosure to the '767 application and the '318
24 patent specification, correct?

1 A Correct.
2 Q And Mizumura is also identical to the
3 '109 patent specification, correct?
4 A That is correct.
5 Q Okay.
6 And I think a couple paragraphs
7 later in paragraph 160, you express the opinion
8 that by April 2019, POSAs would have had reason
9 to -- oh, excuse me.
10 That by April 2019, POSAs would
11 have had a reasonable expectation of success
12 that recombinant Limulus polyphemus Factor C
13 proteins would exhibit the residual activity of
14 claim 21 in view of Mizumura and the '498 PCT,
15 correct?
16 A Yes.
17 Q And then you give some reasons for
18 that expectation in paragraph 178.
19 A Yes.
20 Q And in those reasons, you haven't
21 pointed to any developments in the field
22 between December 2013 and April 2019, other
23 than the publication of the sequence of Limulus
24 polyphemus Factor C, correct?

1 MS. LOUGHRAN: Objection. Form.
2 A That is correct, because the reasons
3 for combining these two specifications had
4 existed, but what was missing was the sequence
5 for Limulus Factor C.
6 And then looking at for the best
7 benefit of residual activity gave another
8 reason for someone to do the combining.
9 Q So if a POSA had the sequence of
10 Limulus polyphemus Factor C in hand before
11 April 2019, they could have compared the
12 sequence to the T. tridentatus Factor C?
13 A They actually had the sequence
14 before, because when we look at McClymont and
15 also the '498 PCT, they were before 2019, but
16 yes.
17 Q Okay.
18 And so at any time if a POSA had
19 the sequence of the Limulus polyphemus Factor C
20 in hand, they could have done that sequence
21 comparison to the T. tridentatus?
22 A Yes.
23 Q And then after doing such a sequence
24 comparison, a POSA would form the expectation

1 that Factor C from Limulus polyphemus and
2 T. tridentatus would be comparable in terms of
3 residual activity?
4 MS. LOUGHRAN: Objection. Form.
5 A I don't -- I don't see that as a
6 conclusion. What I would say -- and I've
7 specified in the declaration, is that a
8 reasonable expectation would be to achieve
9 residual activity somewhere within that broad
10 range that was claimed in claim 21, but not
11 necessarily having the same residual activity
12 profile between Tachypleus and Limulus
13 Factor C.
14 Q Well, in paragraph 182, you state
15 that after a POSA compared the amino acid
16 sequences for the T. tridentatus and the
17 L. polyphemus Factor C, given the similarities
18 overall, such a POSA would expect the two
19 proteins to be comparable in terms of residual
20 activity.
21 That is your opinion, right?
22 A That is. And again, it is about --
23 there's also -- considering that the range for
24 residual activity, that is extremely broad, but

1 overall, we knew all along from 1991, Tokunaga
2 all the way to even 2013 and later that Limulus
3 and Tachypleus Factor C, they have differences
4 in their activity profile.
5 So while they would have
6 differences in the residual activity under the
7 same conditions given the broad nature of the
8 claim, I would expect that Limulus Factor C
9 would fall within the same range as Tachypleus
10 Factor C.
11 I mean, it's 10 percent and
12 15 percent to infinity, so it's like all the
13 way from ground to sky, you can fit anything
14 within that.
15 Q Okay.
16 And that's because the sequences
17 are similar overall, as you wrote in
18 paragraph 182?
19 MS. LOUGHRAN: Objection. Form.
20 A Yes.
21 Q And you didn't do a detailed sequence
22 analysis to support this statement in
23 paragraph 182, did you?
24 MS. LOUGHRAN: Objection. Form.

1 A So when I did the comparison, and not
2 specifically, one of them is actually listed in
3 the declaration, which is a difference around
4 the cleavage site where tryptophan is replaced
5 by valine in Limulus Factor C.
6 But when we look at the
7 catalytic triad of histidine, serine,
8 aspartate, then I saw that to be more similar
9 between Tachypleus and Limulus.
10 So it would give a reasonable
11 expectation for the two to have similar
12 residual activity once a sequence was available
13 for Limulus Factor C, but not necessarily being
14 exactly the same because we already knew all
15 along that the two enzymes have differences in
16 their enzymatic activity.
17 Q All right.
18 So the comparison you just
19 referenced was from the Tokunaga 1991
20 publication?
21 A That is for tryptophan to valine, and
22 that is true when the sequence came out as
23 well.
24 Q Okay.

1 And the similarities around the
2 catalytic triad that you referenced in your
3 prior answer, is that also from Tokunaga?
4 A No, that is from the full sequence,
5 because Tokunaga did not -- they had only a
6 very small chunk of partial sequence.
7 Q And where in your declaration is an
8 analysis of the similarities of the full
9 sequences?
10 A It was -- I did the ExPASy overlay --
11 sequence homology analysis. That's how I
12 looked at the catalytic site.
13 Q That's not in your declaration that's
14 here, Exhibit 1, or in Exhibit 2, is it?
15 A Probably not.
16 Q And this ExPASy overlay is not -- is
17 that a program?
18 A It's a program. It's a well-known
19 program.
20 Q Okay.
21 A It's similar to what Mizumura had
22 used in one of their declarations. I mean,
23 they may or may not have used the same thing.
24 Q Okay.

1 A But they used something likely
2 similar.
3 Q Okay.
4 Earlier in this declaration you
5 opine that a POSA in 2013 would expect that
6 there would be differences in gene and amino
7 acid sequence across different horseshoe crab
8 species.
9 That POSA would have been wrong
10 in view of the actual sequencing data?
11 A So when a POSA is making an
12 assessment, it's based on the information that
13 is available at that time. In 2013 there was
14 no Limulus Factor C.
15 The information that was
16 available to call it a sequence is from
17 Tokunaga paper, and that clearly showed that
18 there is a substitution or a change right next
19 to the cleavage site. There is an
20 N-glycosylation site missing.
21 And these are, in my opinion,
22 some key differences. And if those differences
23 are existing, one cannot know what other
24 differences may exist between the two

1 sequences.
2 And in that scenario, one would
3 rely on the evolutionary knowledge that when
4 the two species are so separated over millions
5 of years, they may have had significant
6 differences in their sequences to have
7 differences in their performance.
8 Moreover, when we look at the
9 Tokunaga paper itself, they have included a
10 graph on the activity of enzymes. There is
11 also data in the '432 patent, which you
12 included in your response to my declaration,
13 that talks about inhibition and enhancement in
14 the presence of different surfactants for -- it
15 was Carcinoscorpius, which is very similar to
16 Tachypleus, and Limulus, and both of those data
17 sets showed that Limulus had a different
18 activity profile than Tachypleus or
19 Carcinoscorpius.
20 So looking in 2013, a POSA would
21 have put all of this information together and
22 concluded that there might -- may be
23 significant differences between the two to be
24 able to assume data on one to apply to the

1 other.
2 Come 2018, now we have the
3 knowledge on the sequence, we can do much more
4 detailed analysis around all the domains that
5 are involved, and even though it doesn't give
6 any confirmation that it would be the same, it
7 at least leads to a degree of reasonable
8 expectation to a POSA to consider that the
9 residual activity could be similar.
10 Q And that's true not just in 2018 but
11 whenever the sequence of L. polyphemus Factor C
12 became available?
13 A Yes, which is 2017 and 2018 for the
14 two sources where it became available, yes.
15 Q And a POSA would have concluded that
16 the residual activity of the two Factor C
17 proteins were similar without the need for
18 experimentation?
19 MS. LOUGHRAN: Objection. Form.
20 A My understanding based on my -- what
21 I've understood the legal terms is that
22 reasonable expectation does not mean an
23 assurance of result. Assurance would only come
24 from experimental verification.

1 So I would say as a POSA, it
2 would be a reasonable expectation which could
3 encourage a POSA to do an experimental
4 verification to get that assurance or not.
5 Q So in paragraph 187 of your IPR
6 declaration, you state that a POSA -- at the
7 end, you say "would have reasonably expected
8 such proteins to exhibit similar values of
9 residual activity as those reported in Mizumura
10 for T. tridentatus," correct? And you don't --
11 Do you see that statement?
12 A Yeah. It's a reasonable expectation.
13 Q And you don't mention the need for
14 any experimentation?
15 MS. LOUGHRAN: Objection. Form.
16 A So what I'm saying is that it's a
17 reasonable expectation. If somebody wants to
18 confirm that reasonable expectation, they would
19 do experimentation.
20 It's not like a POSA needs to do
21 an experimentation to have a reasonable
22 expectation.
23 Q Okay.
24 And then in the next paragraphs,

188 to 190, in view of what you've written in those paragraphs, you agree that a POSA would understand that coinventor Dr. Mizumura had those expectations of similar residual activity based on -- between -- regarding Limulus polyphemus Factor C based on statements he made during prosecution of applications in the '318 patent file history, correct?

MS. LOUGHRAN: Objection.

Q Family. Excuse me.

MS. LOUGHRAN: Objection. Form.

A So if you give me a moment, I want to just read --

Q Yes.

A -- these paragraphs before I...

(The deponent read the document.)

A So it is -- it is in line with what I've stated, that it would be a reasonable expectation and therefore be obvious once the sequence of Limulus Factor C was available.

Q Yes.

A And the question from Dr. Mizumura's declaration is -- okay.

1 Q I'm not asking you about
2 Dr. Mizumura's declaration directly.
3 But I guess my question is, so
4 you agree that a POSA would understand from
5 Dr. Mizumura's statements during prosecution of
6 applications in the '318 patent family that he
7 expected recombinantly produced Limulus
8 polyphemus Factor C would exhibit similar
9 residual activity as the T. tridentatus
10 Factor C?
11 MS. LOUGHRAN: I objected to the
12 form of that question. Thank you.
13 A So again, it goes back to the same
14 thing, that once the Limulus Factor C was
15 available, it would be a reasonable expectation
16 to be able to express and be able to achieve a
17 similar residual activity.
18 The challenge here has been that
19 given the priority date of 2012, and we're
20 using 2013, there was no -- the specific aspect
21 was not and could not have been described and
22 enabled because the Limulus Factor C was not
23 available as of 2013.
24 So even though it was presented

1 by Dr. Mizumura along the prosecution history,
2 it likely was based on the information that
3 became available post 2013.
4 Q When you talk about availability, do
5 you mean published?
6 A Published. Because that is, my
7 understanding, a requirement for it to be
8 described and enabled.
9 Q So having the sequence information of
10 L. polyphemus Factor C would have alleviated
11 the unpredictability of sequence differences
12 between the two proteins sites, because you'd
13 have it?
14 MS. LOUGHRAN: Objection. Form.
15 A It would have addressed that part. I
16 mean, of course it is also the element that
17 the -- the claim is -- of residual activity is
18 excessively broad, and the previous discussion
19 we had on undue experimentation to achieve the
20 full scope of the claim would still be true.
21 But specifically regarding
22 getting some value of residual activity within
23 that range, that would be yes once the Limulus
24 Factor C sequence was available.

1 Q So if the L. polyphemus Factor C
2 sequence was available from public sources in
3 December 2013, then a POSA would have
4 understood the inventors to be in possession of
5 a recombinant L. polyphemus Factor C?
6 MS. LOUGHRAN: Objection. Form.
7 A If the sequence were available, then
8 would a POSA have understood them to be in
9 possession. I would say again it would have
10 remained as a reasonable expectation, because
11 if only the sequence is available and there was
12 no -- neither an example nor a common
13 feature -- and let's also note here that the
14 common feature that was even mentioned for
15 Tachypleus was disclaimed later on for Limulus,
16 so in the absence of an example -- absence of a
17 common feature, I would say it would have still
18 been a reasonable expectation by a POSA to --
19 to have the similar residual activity but not
20 written and described even in that case in 2013
21 if the sequence was available at that point.
22 Q And would you give essentially the
23 same answer for L. polyphemus Factor B and
24 proclotting enzyme?

1 A For Limulus Factor B and proclotting
2 enzyme, they have even greater difference
3 compared to Tachypleus Factor B and proclotting
4 enzyme. They have a low degree of sequence
5 homology. In the case of Factor B, they even
6 have a difference in the number of
7 N-glycosylation sites.
8 So for me to have a reasonable
9 expectation that they would be having a similar
10 activity would be less than that for Factor C.
11 At least in Factor C, you had a
12 similar number of N-glycosylation sites, five
13 and six. But one of the sites that is missing
14 in Limulus is -- was seen by Tokunaga to not
15 be -- and Muta to not be glycosylated.
16 So they're similar glycosylation
17 sites. They're literally a greater degree of
18 homology. Factor B and proclotting enzyme,
19 between the two species have even less,
20 84 percent sequence homology.
21 Q So as of December 2013, there were
22 four known living species of horseshoe crab?
23 A That is correct.
24 Q And the Factor C sequences of two out

1 of those four at least have been published as
2 of December 2013, correct?
3 A That is correct.
4 Q And at least one out of four Factor B
5 sequences have been published?
6 A For Tachypleus, yes, that is correct.
7 Q And the same for proclotting enzyme?
8 A That is correct, for Tachypleus.
9 Q Okay.
10 If you want to turn to
11 Exhibit 2, your PGR declaration. You've got a
12 table on page 28.
13 A Yes.
14 Q And in this table, you calculated
15 that claim 1 includes at least 3,456 possible
16 options or combinations; is that right?
17 A That is correct.
18 Q And you calculated that number based
19 on the three mammalian expression systems
20 listed in the first column?
21 A '767. Based on the '767 application.
22 So these are the three --
23 Q Okay.
24 A I mean, and again, it is -- it is a

1 conservative number. I know 3,000 sounds
2 rather large, but if we strictly look at only
3 claim 1 for Factor B and proclotting enzymes,
4 it says only mammalian cells, which could have
5 been any --
6 Q Understood. Understood.
7 But a POSA could use the same
8 expression vector for many mammalian cell
9 lines, correct?
10 A Yes, they could.
11 Q So you would need two expression
12 vectors for the two Factor C proteins, correct?
13 MS. LOUGHRAN: Objection. Form.
14 A Two expression vectors for two
15 Factor C, or for Limulus and Tachypleus, you're
16 saying?
17 Q Yes.
18 A Okay. Sure.
19 Q And then for each of Factor B and
20 proclotting enzyme, you'd need one expression
21 vector for each version of that -- of those
22 proteins?
23 MS. LOUGHRAN: Objection. Form.
24 A Sure, yes.

1 Q Okay.
2 And it's not your opinion that
3 making ten expression vectors is undue
4 experimentation for a POSA in December of 2013,
5 correct?
6 A If you're strictly talking about only
7 the expression vector and not the transvection
8 and expression and all of that, then yes.
9 But that's not what the -- the
10 claim says.
11 Q Sure. We're taking it a piece at a
12 time, so --
13 A Okay, sure.
14 Q I understand your overall position, I
15 think.
16 You counted the method of
17 recovery, collecting the supernatant or lysing
18 the cells, as two separate options here,
19 correct?
20 A For Factor B and proclotting enzymes,
21 yes.
22 Q How would a POSA determine which
23 method was appropriate for the Factor B and
24 proclotting enzyme proteins?

1 A So it's not about the
2 appropriateness. It's more about depending on
3 the protein, depending on the cell line, what
4 might end up being the outcome.
5 And like I mentioned earlier,
6 that expression of protein is dependent on a
7 multitude of factors, and depending on the
8 protein and the cell line and the culture
9 conditions, it could get secreted or it may not
10 get secreted.
11 I mean, we saw that example, for
12 example, with factor -- Carcinoscorpius
13 Factor C expressed in COS-1 cells, where it did
14 not get secreted.
15 So depending on those factors,
16 we have to consider both scenarios, that a
17 protein may get secreted, it may not get
18 secreted. Secreted protein is certainly
19 preferable, but it may not necessarily be
20 always happening in every scenario.
21 Q Sure.
22 But to figure out where the
23 protein is being, you know -- where the protein
24 can be recovered from is either you look at

1 it -- look for it in the supernatant or you
2 lyse the cells and look for it there?
3 A Yeah.
4 MS. LOUGHRAN: Objection. Form.
5 A And I think they did that in one of
6 the papers where they looked at supernatant,
7 lysate and pellet, which was the leftover solid
8 material, and they looked for where the protein
9 is located.
10 So if the -- if the POSA doesn't
11 see the protein in supernatant, then the
12 natural tendency would be to lyse the cells and
13 look for them there. Or go back and keep
14 optimizing the cell culture conditions, so
15 vector and all of those, to see how they can
16 get the protein to be secreted.
17 Q Does claim 1 require going back to
18 optimize the cell culture conditions?
19 MS. LOUGHRAN: Objection. Form.
20 A It doesn't say anything, so the
21 protein could be secreted, it could be present
22 intracellularly. And that's why we have all
23 these recovery conditions included as -- for
24 the calculation of the combinations.

1 Q And I believe you stated elsewhere in
2 your declaration that these 3,456 possible
3 combinations involved at least 54 proteins?
4 A Yes.
5 Q And so it's your opinion that, for
6 example, Factor B made and expressed in CHO
7 cells is a different protein than one made
8 using the same vector but expressed in CHO DG44
9 cells?
10 MS. LOUGHRAN: Objection. Form.
11 A So from a sequence perspective,
12 they're not different protein. They're the
13 same protein. However, as has been seen even
14 by the inventors, that the cellulation of the
15 protein -- or the glycosylation of the protein
16 could have an impact on the activity of the
17 enzyme.
18 But it's not about having a
19 different protein only. It's also looking at
20 the full scope of the claim, and the claim has
21 set of steps. The first step is to be able to
22 express it, and then be able to put it together
23 as a cascade. And therefore, from a steps
24 perspective, expressing protein in CHO cells,

1 the same -- Tachypleus in CHO cells versus
2 Tachypleus in HEK293 would be two different
3 activities.
4 Q Oh, I see. By "activities," you mean
5 like experiments, not --
6 A Yes.
7 Q Not functional activities?
8 A Not a functional activity, but yes.
9 Q Okay.
10 A It's like the procedure or the steps.
11 Q Right.
12 A Something like that, yeah.
13 Q Okay.
14 A But experiments we can say.
15 Q Sure.
16 And these are -- this type of
17 experiment, creating a vector and expressing it
18 in a cell line, is not an experiment that
19 you've ever done?
20 MS. LOUGHRAN: Objection. Form.
21 A So I've -- I've done the second part.
22 So when you are expressing protein, there is
23 one element of transvection. The other one is
24 of having the protein -- the cells being

1 cultured and protein being secreted.
2 So I have been more involved
3 with taking the cell line from the cell line
4 development group and then doing the
5 secretion -- culturing the cells and secreting
6 the protein.
7 So I've been -- it's two parts
8 usually in an industrial setting done by two
9 different groups, large teams. So I've been
10 part of one element of that out of the two
11 elements.
12 Q Okay.
13 So continuing on in Exhibit 2,
14 your PGR declaration, I believe in
15 paragraph 111, you're expressing the opinion
16 that the '76- -- I'll wait until you're there.
17 A You said 111?
18 Q Yeah.
19 It's your opinion that the '767
20 application provides no guidance or teaching as
21 to how a POSA would make or use Factor B
22 proteins within the scope of claim 1?
23 MS. LOUGHRAN: Objection. Form.
24 A Yes, in mammalian cells, yeah.

1 Q And you have the same opinion with
2 respect to proclotting -- expressing
3 proclotting enzyme in mammalian cells?
4 MS. LOUGHRAN: Objection. Form.
5 A That is correct.
6 Q And if you turn to paragraph 193 in
7 your PGR declaration.
8 A Okay, last page.
9 Q Yeah.
10 In contrast to your opinions
11 about the '767 application, it's your opinion
12 that the '629 publication has detailed
13 directives for assembling Factor C, Factor B
14 and proclotting enzyme into an endotoxin assay
15 agent, as recited in claim 1 of the '109
16 patent?
17 MS. LOUGHRAN: Objection to
18 form.
19 A So let me elaborate a bit on that.
20 So what I'm claiming in paragraph 193 is the
21 '629 specification shows one example out of
22 those nearly 3,500 or more combinations that
23 were in table on page 28.
24 So for that reason, I'm claiming

1 anticipation by '629 specification for claim 1.
2 Now, to your specific comparison
3 between 111 and 193, in '767 application,
4 Tachypleus Factor C was produced in CHO and HEK
5 cells. However, the Factor B and proclotting
6 enzymes both were in the Sf9 insect cells.
7 In '629 specification, the
8 inventors have used Limulus Factor C, Factor B
9 and proclotting enzyme, and they were able to
10 express them -- they expressed all three of
11 them in CHO cells. They put them together and
12 were able to show that they were functional as
13 well.
14 So when I look at '629
15 specification, that example is able to meet
16 each and every sentence in claim 1 of '109
17 specification, whereas Tachypleus -- whereas
18 '767 application does not meet much of the
19 content of claim 1 in '109 specification.
20 Q So it's a matter of providing an
21 example as opposed to the level of detail of
22 the instructions provided in the two
23 references?
24 MS. LOUGHRAN: Objection. Form.

1 Misstates testimony.
2 A You're saying about '767, right?
3 Q Yes, between the '767 and the '629
4 publication, it's the example in the '629
5 publication --
6 A It's actually --
7 Q -- that you find sufficient?
8 A Sorry. It's actually two things.
9 One is for '767, yes, there is no example for
10 Factor B and proclotting enzyme in mammalian
11 cells, or a common feature that could say if
12 this is present, which my experience is that
13 one -- we still don't know a common feature
14 that tells from a sequence to expressability in
15 mammalian cells. So that is one element.
16 But then we also have to
17 remember that claim 1 in '109 specification is
18 excessively broad, that allows all the mixing
19 and matching of different host cells -- protein
20 expressed in different host cells from
21 different species. Even if I look at claims 1
22 to 9, even then it's like 864 combinations.
23 So even if '767, to your point,
24 had included an example of Tachypleus Factor B

1 and Tachypleus proclotting enzyme expressed in
2 mammalian cells, and then put together as a
3 cascade, that still would have been one example
4 among thousands of combinations within the
5 scope of -- or if I look 1 to 9, there are 864
6 combinations, still would have been only one
7 example. It wouldn't have described or enabled
8 the full scope of the claim.
9 Q So in paragraph 193 when you use the
10 phrase "detailed directives of the '629
11 publication," the difference between the '629
12 publication and the '767 application is because
13 of the inclusion of an example in the '629 as
14 opposed to the level of detail in the
15 instructions in the two specifications?
16 MS. LOUGHRAN: Objection. Form.
17 A Yeah, essentially it's about having
18 an example that would -- that describes and
19 enables, for that specific example, specific
20 case of Limulus Factor B and proclotting
21 enzyme.
22 Q So it's not that the '629 publication
23 includes much more detailed instructions on how
24 to make the -- the vectors and express the

1 protein in comparison to the '767 application?
2 MS. LOUGHRAN: Objection. Form.
3 A That is correct, and that is why I
4 consider that to be a case of anticipation
5 than -- than anything else, because that
6 example is specific to Limulus Factor B and
7 proclotting enzyme that cannot be translated to
8 other horseshoe crab, Tachypleus Factor B and
9 proclotting enzyme.
10 Q So you agree that a POSA would view
11 the level of details of the instructions for
12 expressing Factor B and proclotting enzyme to
13 be similar in the '629 publication and the '767
14 application?
15 MS. LOUGHRAN: Objection. Form.
16 A They would have wanted or they
17 would -- they would --
18 So I'm trying to understand. So
19 there is no similarity for Factor B and
20 proclotting enzyme between '629 and '767. So
21 what -- what are you -- so if you could just
22 elaborate on your question.
23 Q Yes.
24 So you say that the '629

1 publication includes detailed directives,
2 correct?
3 A Yes.
4 Q And the '767 application also
5 includes directives, just less detailed, in
6 your opinion?
7 MS. LOUGHRAN: Objection. Form.
8 A It only includes for Factor C. It
9 does not include for Factor B and proclotting
10 enzyme in mammalian cells.
11 Q But do you recall that the '767
12 application says that the methods applied for
13 expressing Factor C can be applied mutatis
14 mutandis to Factor B and proclotting enzyme?
15 A Just because it says that doesn't
16 mean that void of protein expression, it
17 necessarily happens. And I've been saying this
18 throughout the day, that protein expression is
19 dependent on a multitude of factors, and just
20 because a certain procedure works for one
21 protein and one cell line does not mean that it
22 would work for another protein, especially also
23 considering that Factor C and Factor B and same
24 proclotting enzyme are extremely different

1 proteins.
2 Q But you don't know whether or not
3 that "mutatis mutandis" statement in the '767
4 application is based on experimental
5 experiments that the inventors did or not,
6 right?
7 MS. LOUGHRAN: Objection. Form.
8 A I don't know if they did any
9 experiments or not, but if they did, none of
10 the statements are suggestive of they having
11 done those experiments.
12 And if they had done it, why did
13 they not include any of those examples? If not
14 in '767, at least they could have bothered to
15 include it in '109. They didn't even care to
16 include that.
17 Q But it's your assumption that that
18 statement is not backed up by actual
19 experiments that the inventors had conducted?
20 MS. LOUGHRAN: Objection. Form.
21 A That's -- I mean, it -- you can call
22 it an assumption, but if there is a claim that
23 calls out for Factor B and proclotting enzyme
24 in mammalian cells and there is not a single --

1 not even just about expression. They did not
2 even -- if they had not even disclosed
3 expression but they had at least put together
4 the three mammalian expressed factors into a
5 cascade and shown that this is the result, then
6 at least it would have been clear that yes,
7 they possessed the invention, and they just did
8 not describe how they express it.
9 But it's not just even limited
10 to expression. They didn't even put it
11 together as a cascade when the claim requires
12 it, the three mammalian expressed factors to be
13 put together as a cascade.
14 So the claim and any content in
15 '109, '767, any of those things just don't
16 match.
17 MS. LOUGHRAN: We've been going
18 for about an hour, counsel.
19 MS. LO: Yeah, we can take a
20 break.
21 MS. LOUGHRAN: Okay.
22 (Recess.)
23 (Exhibit 6 marked for
24 identification.)

1 BY MS. LO:
2 Q All right. We're back on the record.
3 Dr. Jain, I'm going to hand you
4 what we've marked as Jain Exhibit 6. It's CRL
5 Exhibit 1015 from the PGR.
6 A Thank you.
7 Q And do you recognize this document,
8 Exhibit 6?
9 MS. LO: Oh, I'm sorry.
10 MS. LOUGHRAN: Thank you so
11 much.
12 A Yes, '629 specification.
13 Q Okay.
14 And do you understand that
15 sequence ID No. 5 in this publication is
16 Factor B from Limulus polyphemus? You can look
17 at paragraph 181.
18 A Let's look at the sequence. Yes,
19 that is correct.
20 Q Okay.
21 And then paragraph 194 informs
22 us that SEQ ID No. 13 is proclotting enzyme
23 from L. polyphemus?
24 A What sequence did you say?

1 Q 13.
2 A That is correct.
3 Q And in paragraph 350, the '629
4 publication states that these two cDNA
5 sequences, SEQ ID No. 5 and 13, were ligated to
6 vector pCA7, correct?
7 A That is correct.
8 Q And the pCA7 vector was available
9 before 2015, correct?
10 A That is my understanding.
11 Q And it was in fact available well
12 before 2013, correct?
13 MS. LOUGHRAN: Objection. Form.
14 Q Withdrawn.
15 And it was available as of 2005,
16 at least 2005, correct?
17 MS. LOUGHRAN: Objection. Form.
18 A I'm not exactly familiar with 2005,
19 how long before it was available, but certainly
20 to your first question, available 2015, yes.
21 Q It you look at paragraph 343 in
22 Exhibit 6, there's a reference to expression
23 vector pCA7.
24 A Yes.

1 Q And a parenthetical citation to a
2 paper by Takeda et al. dated 2005?
3 A I see that reference.
4 Q So based on that citation, you would
5 understand that pCA7 was available as of at
6 least 2005, correct?
7 MS. LOUGHRAN: Objection. Form.
8 A Sure.
9 Q And so going back to paragraph 350,
10 it says that the ExpiCHO expression system was
11 used to express Factor B and proclotting
12 enzyme, correct?
13 A That is correct, and Factor C as
14 well.
15 Q And Factor C. And that expression
16 system uses CHO cells, right?
17 A That is correct.
18 Q And CHO cells had been used to
19 express proteins long before 2019, correct?
20 A That is correct.
21 Q And is this paragraph 350 the -- part
22 of the detailed directives you were referring
23 to in paragraph 193 of your declaration that we
24 were looking at before the break?

1 MS. LOUGHRAN: Objection. Form.
2 A That is correct.
3 Q Okay.
4 A This one and the subsequent one, 351
5 on the...
6 Q Okay.
7 And in paragraph 359, the '629
8 publication also states that pCI-neo can also
9 be used to express L. polyphemus Factor C,
10 correct?
11 A That is correct.
12 Q And do you recall that the '109
13 patent, the one at issue in the PGR, also
14 discloses using pCI-neo to express a Factor C
15 protein?
16 MS. LOUGHRAN: Objection. Form.
17 A Yes, that was present in '767
18 application as well.
19 Q And the '767 application also teaches
20 use of the pCA7 vector also, correct?
21 A That is correct, that was used for
22 HEK293.
23 Q Let's see. We can go back to your --
24 MS. LO: Well, let's mark as

1 Exhibit 7 -- this is Exhibit -- it's CRL
2 Exhibit 1006, and I believe that's the IPR
3 number.
4 (Exhibit 7 marked for
5 identification.)
6 BY MS. LO:
7 Q Do you recognize --
8 A They need a copy.
9 MS. LO: Apologies for the size
10 of the stack as well as the lateness.
11 MS. LOUGHRAN: We're no stranger
12 to paper around here.
13 BY MS. LO:
14 Q Okay.
15 And do you recognize Exhibit 7
16 as the '767 application as filed?
17 A I do.
18 Q Okay.
19 And then if you can turn in
20 Exhibit 2, your PGR declaration, and just
21 verify that this is the same document that was
22 used as Exhibit 1017 in the PGR?
23 A That is correct.
24 Q Okay.

1 And staying in your -- in
2 Exhibit 2, your PGR declaration, in
3 paragraph 51, the footnote, you noted that --
4 in footnote 1 you noted that a paragraph was
5 added to the '767 application?
6 MS. LOUGHRAN: Objection. Form.
7 Q Oh, excuse me. That a paragraph was
8 added in addition to the '767 application?
9 A It was added in '767 application,
10 which was not in the prior PCT.
11 Q Yes, thank you. Okay.
12 And that -- and you reproduced
13 that paragraph in footnote 1 of Exhibit 2,
14 correct?
15 A Yes, it was more for the sake of
16 completeness so that we are looking -- basing
17 our assessment on the universe of information
18 in the specification, not missing anything.
19 Q And the information added in that
20 paragraph was known before December 10, 2013,
21 correct?
22 MS. LOUGHRAN: Objection. Form.
23 A Let me just read it.
24 Q Mm-hmm.

1 (The deponent read the
2 document.)
3 A Yes.
4 Q Okay. All right.
5 So let's turn to Exhibit 7. And
6 if you can go to page 50 --
7 A 50?
8 Q Sorry. Just a minute.
9 MS. LO: Sorry, can we go off
10 the record?
11 MS. LOUGHRAN: Sure.
12 (Discussion off the record.)
13 BY MS. LO:
14 Q Okay. Dr. Jain, I'd like to direct
15 your attention to paragraph 107 of Exhibit 2,
16 your PGR declaration.
17 You can leave -- we'll go back
18 to the big one.
19 A So I should keep both?
20 Q Yes, keep that one out, but go to
21 paragraph 107 of Exhibit 2 for now.
22 A 107.
23 Q And in paragraph 107, you're actually
24 quoting from Exhibit 7, correct?

1 A Yes.
2 Q And -- and you're quoting the
3 statement about mutatis mutandis we touched on
4 earlier, correct?
5 A That is correct.
6 Q What is your general understanding of
7 what that phrase means?
8 A My understanding in a non-legal
9 simplistic manner is that the procedure or
10 protocol that was applied for one thing can be
11 used as it is to get the desired outcome or
12 same outcome with a second or third item.
13 In this case, the protocol that
14 was used for expressing Tachypleus Factor C can
15 be used as it is to obtain secreted and
16 functional Tachypleus Factor B and Tachypleus
17 proclotting enzyme.
18 Q Okay.
19 And in this same paragraph, you
20 opine that a POSA in the field of recombinant
21 protein production would not assume the
22 translatability of the expression process
23 across proteins.
24 MS. LOUGHRAN: Objection. Form.

1 A That is correct.
2 Q So if translatability cannot be
3 assumed -- and a POSA would not assume this, as
4 you say -- then wouldn't a POSA believe that
5 the inventors were also not just assuming this
6 translatability?
7 MS. LOUGHRAN: Objection. Form.
8 A So it can be looked at in two
9 different ways, and the way I interpret it was
10 that the inventors made a generalization
11 without necessarily possessing
12 mammalian-expressed Tachypleus Factor B and
13 mammalian-expressed Tachypleus proclotting
14 enzyme in '767 application.
15 Q And that's based on the lack of
16 examples.
17 A Lack of example and specifically if I
18 go to '109, not even an attempt to put together
19 one cascade with all three proteins coming out
20 of the mammalian expression, which is the core
21 of claim 1.
22 Q You don't cite a reference here about
23 the translatability of expression processes
24 across proteins in paragraph 107 of your

1 declaration, correct?
2 A It is primarily coming out of my
3 experience, experiences. If you'd like to
4 hear, like --
5 Q I --
6 A Okay.
7 Q And your experience in translating
8 from insect cells to mammalian cells was one
9 protein?
10 MS. LOUGHRAN: Objection. Form.
11 A So insect to mammalian was one, but
12 also looking at the expression of similar
13 proteins in CHO cells or HEK293 cells with the
14 same cell culture conditions but seeing very
15 different expression profile to the point of
16 some of the proteins not even expressing, or
17 aggregating after expression.
18 So based on my -- both
19 experiences, I concluded -- and, like I said,
20 even why I mention it in the paper, and if you
21 read any publications regarding mammalian
22 expression, you will see the same theme.
23 There's a reason why there are
24 large cell line development and process

1 development teams within the biopharmaceutical
2 industry. If it was that simple and
3 straightforward, then we could have just
4 expressed the protein and have a process very
5 quickly.
6 Q But you don't cite any of those
7 publications here in paragraph 107?
8 MS. LOUGHRAN: Objection. Form.
9 Q I mean, it's a simple -- right?
10 There's no citation there?
11 A No, I do not.
12 Q Okay.
13 A And I relied on my direct experience
14 also in this instance.
15 Q Okay.
16 And are you aware of any
17 publications that described difficulties in
18 expressing Factor B or proclotting enzyme in a
19 mammalian expression system?
20 A Factor B and proclotting enzyme? No,
21 I'm not aware.
22 The only instances I've seen of
23 expressing those two proteins, to my
24 recollection at this point, comes from a

1 Kobayashi paper and then '629 specification.
2 Q Okay.
3 Now let's turn to Exhibit 7,
4 which is the '767 application.
5 A Okay.
6 Q If we can go to paragraph 113, which
7 is on page 87, according to the added footer.
8 A Page 87.
9 Q The added footer, not the internal.
10 A Oh, okay.
11 MS. LOUGHRAN: This.
12 A I see. I see.
13 Q Yes, yes.
14 A I'm needing my glasses more today.
15 Okay.
16 Q Okay.
17 So this is where an example
18 starts describing the expression of Factor C in
19 HEK293 cells, correct?
20 A That is correct.
21 Q The inventors used PC -- the pCA7
22 vector, correct?
23 A For HEK293, yes. It's the second to
24 last line.

1 Q And they describe it as a vector for
2 expression in mammalian cells, plural, correct?
3 A That is correct.
4 Q And so you would agree that the '767
5 application informs a POSA that this pCA7
6 vector can be used to express Factor B and
7 proclotting enzyme as well because of the
8 mutatis mutandis statement?
9 MS. LOUGHRAN: Objection. Form.
10 A I think it goes back to again the
11 whole generalization of protein expression.
12 Vector is not the only driving factor for
13 expressing protein. If the protein needs a
14 certain degree of glycosylation, or it needs
15 specific chaperones, or the protein has a
16 propensity to aggregate. It also depends on
17 where the gene may be integrating.
18 So a lot of those factors are
19 there. I mean, it's -- vector is one element.
20 And if I use an analogy that's
21 going to your point, when Roopashree and Ding
22 tried to express Carcinoscorpius Factor C in
23 COS-1 cells, they used pCI-neo as a vector,
24 which is listed here as well.

1 They used DMEM media with
2 10 percent FBS, which is the media that was
3 used for HEK293 cells here. So same
4 conditions. Just the cell line is different.
5 The protein is different. And they got a very
6 different result.
7 So maybe it was a single
8 sequence. Could be the protein, could be the
9 cell line. But that is one example that
10 highlights how complex protein expression,
11 successful protein expression is.
12 And therefore, this mutatis
13 mutandis doesn't actually work without doing
14 experimental verification and, if needed,
15 optimization of cell culture -- of a process,
16 protocol.
17 Q So that Dwarakanath paper you
18 referenced was from 1997, correct?
19 A Yes.
20 Q And the inventors successfully
21 expressed Factor C in mammalian cells as
22 described in the '767 application, correct?
23 A But I just highlighted, because you
24 were saying -- talking about vector as being

1 important. They used the same vector, pCI-neo,
2 which was used for CHO cells here. They used
3 the same media that they used for HEK293.
4 So that's what I'm getting at,
5 that even if you have the same vector, it does
6 not mean that the protein will express.
7 And the questions are focusing
8 on the vectors, so I'm just highlighting that
9 part, the vector is one part of the whole
10 story. It's not the whole story.
11 Q Okay.
12 So going back to Exhibit 7, the
13 '767 application, in paragraph 129, which
14 starts at the very bottom of external page 93,
15 this paragraph describes testing the activity
16 of an assay using recombinant Factor C,
17 recombinant Factor B, and recombinant
18 proclotting enzyme, correct?
19 A That is correct.
20 Q All right.
21 Let's move on and mark as
22 Exhibit 8 Tab 4.
23 A Should I keep 7 open or for now --
24 Q You can put that aside, yeah.

1 MS. LO: So we'll mark as
2 Exhibit 8 CRL Exhibit 1005.
3 (Exhibit 8 marked for
4 identification.)
5 MS. LOUGHRAN: Thank you.
6 BY MS. LO:
7 Q And, Dr. Jain, can you just confirm
8 that Exhibit 8 was submitted as Exhibit 1005 in
9 both the IPR and the PGR?
10 (The deponent read the
11 document.)
12 A Yes, 1005 from PGR.
13 Q It's just housekeeping for the
14 record, but thank you.
15 So what is Exhibit 8?
16 A It's the -- my understanding is it's
17 the international application that described
18 for the first time, as per the inventors, the
19 full cDNA and amino acid sequences of Limulus
20 Factor C, Factor B and proclotting enzyme, and
21 this eventually led to the '629 specification.
22 Q Okay.
23 And so this is -- you refer to
24 Exhibit 8, which is WO 2018/074498 as the '498

1 PCT in your declarations?
2 A That is correct.
3 Q And the PCT application that was
4 published as Exhibit 8 claims priority to a
5 Japanese application that was filed on
6 October 18, 2016; is that correct?
7 A Yes, I see that on the face of the
8 application.
9 Q Okay.
10 And you quoted statements from
11 Exhibit 8 in your declarations, correct?
12 A That is correct.
13 Q And did you happen to look at the
14 Japanese priority application as part of your
15 work on this case?
16 A I don't recall.
17 Q Okay.
18 So --
19 A I mean, this is the submitted
20 application, so I think this might -- this
21 would matter more than the provisional
22 application.
23 Q Why do you say that?
24 A I mean, this is the submitted full

application, right, for the international patent submission, so -- so if I looked at it, this should be sufficient.

Q So you don't know one way or the other if the Japanese priority application included the same list of sequences?

MS. LOUGHRAN: Objection. Form.

A No, I don't.

Q All right.

So I wanted you to have Exhibit 8 to refer to if you'd like but it might be easier if we turn back to Exhibit 2, your PGR declaration where you quote Exhibit 8.

So, for example, in Exhibit 2, paragraph 66, you're quoting paragraphs 4 to 13 of the '498 PCT, correct?

A That is correct.

Q And it's your opinion that the inventors could not have described an example of Limulus polyphemus Factor C, Factor B and proclotting enzyme because the sequences were not disclosed in the art as of the priority date, correct?

A Because they would not -- yes, they

1 were not determined as of 2013.
2 Q You said they were not yet disclosed.
3 Is there a difference between
4 disclosed and determined?
5 A So from a description and enablement,
6 it is disclosed. However, when I also look at
7 the '498 application and the reference to the
8 whole genome project, which became public in
9 2014, suggests that this work was conducted
10 after the whole genome sequence was available.
11 So if you look at -- if you look
12 at paragraph 13, it talks about a comprehensive
13 analysis of the genes of Limulus polyphemus is
14 being conducted as part of the invertebrate
15 genome project using next-generation sequences.
16 And then it talks about they
17 have not been elucidated, and it also
18 demonstrates the difficulty in accurately
19 determining.
20 Q So you were just reading from
21 paragraph 13 of Exhibit 8.
22 A That is correct.
23 Q Okay.
24 And the genome project

1 referenced in paragraph 13 was published as of
2 January 2014 according to Dr. Frohman, correct,
3 which you verified?
4 A That is correct.
5 Q And we established that Ms. McClymont
6 obtained prerelease access to that genomic
7 data, correct?
8 MS. LOUGHRAN: Objection. Form.
9 A That is correct.
10 Q So we can stay in Exhibit 7.
11 Is that what you have open in
12 front of you?
13 A I need --
14 Q I'm sorry, Exhibit 8. Okay.
15 So Exhibit 8. And you've quoted
16 from --
17 A Paragraph 13.
18 Q Excuse me?
19 A I quoted paragraph 13.
20 Q Yes, okay.
21 And going back to your
22 declaration, your IPR declaration in -- excuse
23 me, your PGR declaration in paragraph 67,
24 you've included some direct quotes from the

1 '629 publication.
2 A That is correct.
3 Q And do you see the phrase "proteins
4 involved in a mechanism"?
5 A In 67?
6 Q Yes.
7 (The deponent read the
8 document.)
9 A Yeah, in the middle, "because
10 proteins involved in a mechanism of occurrence
11 of clotting"?
12 Q Yes.
13 What is your understanding of
14 the proteins that are referenced by that
15 phrase?
16 A My understanding is that it is
17 referring to Limulus Factor C, Factor B and
18 proclotting enzyme.
19 Q Okay.
20 A Because these are the three
21 proteins -- and coagulogen. Specifically these
22 three, because coagulogen sequence was -- my
23 recollection is it was -- it was known before,
24 but these three were not.

1 Q And is that also your understanding
2 of the proteins and genes referenced in the --
3 later in that sentence, "complete
4 identification of these proteins and genes from
5 both structural and functional aspects"?
6 Your understanding is that
7 "proteins and genes" refers to --
8 A The three factors.
9 Q Okay.
10 A From Limulus.
11 Q And the same three factors referenced
12 in the phrase "proteins and genes" right before
13 the page break at the bottom of page 32?
14 A That is correct.
15 Q That sentence continues to
16 reference -- it continues and references
17 general techniques. Do you see that?
18 A That is -- yeah, I see that.
19 Q What is your understanding of the
20 general techniques that the authors are
21 referencing there?
22 A So my understanding by "general
23 techniques" would be the techniques that had
24 been available in the '90s and early 2000s that

1 were used for Tachypleus, Carcinoscorpius
2 sequencing that were based on standard reverse
3 transcriptase -- transcription to get the cDNA
4 sequence. So that is what I'm interpreting it
5 as.
6 Q So when you wrote this declaration,
7 Exhibit 2, you didn't understand "general
8 techniques" to include RACE PCR?
9 MS. LOUGHRAN: Objection. Form.
10 A So when we look at Dr. Frohman's
11 declaration, we have to understand that it's
12 not just about the use or not use of RACE
13 technology, because that's -- that's somewhat
14 of an opinion focused only on the sequencing of
15 mRNA.
16 There are other elements that
17 are involved in sequencing the Factor C,
18 Factor B and Tachy -- and proclotting enzyme
19 mRNA. And the complexities might have been
20 related to other challenges, not just related
21 to what specific sequencing methodology was
22 used.
23 So, for example, when you look
24 at the '498 PCT or '629 specification, the

1 inventors noticed that one of the PCR products
2 did not actually show in the gel, and they
3 found what -- the terminology they used -- I
4 could check that -- was something like
5 "nonspecific amplification" or something.
6 Now, it could be because the PCR
7 had an issue, but it could also mean that the
8 quality and quantity of mRNA that was obtained
9 from Limulus -- Limulus blood was of not the
10 same degree as the Tachypleus, and that could
11 relate to the differences in diversity that the
12 inventors talk about.
13 There are also other challenges
14 like -- that we already see in '419 PCT,
15 existence of variance due to polymorphism, and
16 also it was known that because a whole genome
17 duplication in Limulus, there were instances of
18 paralogs. So being able to identify those
19 variants could have added to the complexity.
20 So the inventors don't go into
21 the specific details of whether the techniques
22 are pertaining to the sequencing aspect, or
23 being able to deal with potentially a different
24 quality and quantity of mRNA, or the presence

1 of different variants.
2 But it's clear from their
3 procedure that from -- there was some
4 differences, some challenges that they faced
5 with regards to getting amplification -- DNA
6 amplification.
7 Q When you reviewed the '629
8 publications, did you recognize that the
9 inventors used the RACE PCR technique to clone
10 Limulus Factor C?
11 MS. LOUGHRAN: Objection. Form.
12 A So it was not explicitly listed.
13 What is interesting -- and it's a pure
14 speculation, so I want you to be aware of that,
15 is that when we go to the examples -- I need to
16 find that page for examples.
17 Q Well, I think it's a fairly simple
18 answer.
19 If you weren't aware of the RACE
20 PCR technique until it was raised in the patent
21 owner's preliminary response that was served a
22 few months ago, then you couldn't have
23 recognized it from the '629 --
24 MS. LOUGHRAN: Objection. He's

1 trying to answer your last question.
2 A Give me a moment. I'm just trying to
3 find the -- where the examples start.
4 I can't find an example.
5 Q Page 36?
6 A Page 36. Thank you.
7 So when you look at -- so what I
8 did see was that in paragraph 151 where they
9 list the primers, one of the primers, if you
10 will see, is listed as LFC-5race.
11 So it's a speculation, because,
12 again, like I said, I'm not an expert in RACE
13 technique, but when I saw that, that was
14 suggestive, that possibly the inventors may
15 have used a RACE primer in their work.
16 But, again, like I said, it's a
17 speculation that I had.
18 Q But you testified earlier that you
19 weren't aware of the RACE PCR technique until
20 it was raised after you prepared your
21 declaration in these matters?
22 A Yes. And I'm saying that when I was
23 reviewing as part of this deposition, I noticed
24 that they are listing -- marking one of the

1 primers as RACE, which could be suggestive, but
2 it's speculative that the inventors might have
3 used RACE technique, at least in one step of
4 determining the sequence.
5 Q Thank you for clarifying the timing
6 of that. Okay.
7 All right. Let's go back to
8 Exhibit 2, your PGR declaration, paragraph 88.
9 A Okay.
10 Q And you've also quoted from the '629
11 publication here, correct?
12 A Yes.
13 Q So in the middle of the quote,
14 there's a phrase "complete identification."
15 Do you see that?
16 A I do.
17 Q What is your understanding of that
18 phrase?
19 (The deponent read the
20 document.)
21 A So the way I interpret it was that
22 the full amino acid and gene sequence was not
23 available even 20 years after the Tachypleus
24 and Carcinoscorpius Factor C sequences were --

1 were available.
2 If I look at it literally,
3 they're talking about structure and function,
4 and the function of the proteins were known but
5 the structure was not elucidated by -- even in
6 this specification, '629.
7 So that is why my interpretation
8 was that they're referring to the full amino
9 acid and gene sequence of the three Limulus
10 factors.
11 Q And the three tridentatus factors had
12 been identified by 1991?
13 A Somewhere in that time frame, '91,
14 '92, something like that.
15 Q And continuing on in the quote, it
16 references various differences and diversity of
17 biomolecules; do you see that?
18 A I do.
19 Q And what was your understanding of
20 the differences referenced in this statement?
21 A So as I just described, that
22 evolutionarily, it was known that Limulus
23 polyphemus and Tachypleus tridentatus have
24 differences, and in fact there are articles

1 that I've mentioned, the differences even
2 within the local geography of horseshoe crabs,
3 the genetic differences.
4 Specific to this, my
5 interpretation was that they're referring to
6 the differences in diversity of biomolecules
7 being that the molecules are different, the
8 mRNA expression level is different, the degree
9 of variants and paralogs that could be present
10 are different.
11 And all of those differences and
12 the diversity between the horseshoe crabs would
13 pose challenges to have the full sequence for
14 Limulus factors as opposed to Tachypleus
15 factors.
16 Q How would the inventors know that the
17 mRNA expression levels are different across
18 species?
19 A So one way to know how -- what the
20 mRNA level is to be able to do the -- to be
21 able --
22 One way I believe they could
23 have seen the level was different is just the
24 fact that when they -- that there was

1 transcription and tried to do the
2 amplification -- and it's somewhere in the
3 example. Their first PCR product was not
4 visible on the gel, and they mentioned that it
5 was nonspecific amplification they saw.
6 And that could very well be
7 because of lower level of mRNA expression for
8 Factor C. Let me see if I can find that.
9 Q I think I know what you're referring
10 to.
11 A I think it was the LpFC1. It's in
12 158.
13 Q Oh, okay.
14 A Or something like that.
15 Q And how would a POSA know that there
16 were differences in mRNA expression levels and
17 degree of variants and paralogs?
18 MS. LOUGHRAN: Objection. Form.
19 A So I don't think someone would know
20 unless they would attempt to test it
21 experimentally. There is no information that
22 would be available beforehand.
23 I mean, one way indirectly one
24 can try to estimate is that the protein

1 expression level is at times correlated to the
2 mRNA level, so one can look at what is the
3 level of Limulus Factor C versus Tachypleus
4 Factor C.
5 But that can also be variable
6 from organism to organism, so at the end of the
7 day, it would have to be assessed
8 experimentally.
9 Q And are you aware of any publications
10 describing failed attempts to determine the
11 sequence of the Limulus polyphemus three
12 proteins?
13 A So I'm not aware of any failed
14 attempts. But you also have to understand how
15 the scientific publication world works, that we
16 rarely see a publication -- and this has been
17 an ongoing discussion for a while -- that the
18 scientific world rarely publishes failed
19 results. And in fact the system doesn't
20 encourage publication of failed results.
21 So if it's not published doesn't
22 mean that there is no failure, but the world
23 will not know if there was a failed attempt or
24 not. And it's simply -- it could be based on

1 either nobody had attempted but it could very
2 well be because failed attempts are rarely
3 published.
4 Q And along -- in the same vein, if
5 it's not published, if something is not
6 published, it doesn't mean -- withdrawn.
7 If a sequence is not published,
8 it doesn't mean that it hasn't been determined
9 or it is not possible to determine, right?
10 MS. LOUGHRAN: Objection. Form.
11 A So I think we need to go back to the
12 fundamental aspect of my declaration, that was
13 the -- was claim 1 or claims 1 to 9 described
14 and enabled as of 2013. So even if the
15 inventors had access to Limulus sequences, they
16 did nothing to ensure that a POSA would be able
17 to assess that the inventors were truly in
18 possession of the invention, and it is simply
19 because they did not describe anything.
20 Did they enable? If they don't
21 publish, they keep it secretly to themselves,
22 they did not enable a POSA to be able to make
23 use of the -- the invention.
24 And then moreover, I mean, we

1 have talked about it, that there are so many
2 combinations. It's not even about just
3 Limulus. We are focused on Limulus, but it's
4 also about the combinations and everything,
5 which certainly has not been done.
6 So yes, maybe, to your point, if
7 the inventors did not disclose but they had it,
8 but my understanding, not being a lawyer, is
9 that the patent doesn't mean that you can have
10 it but not tell people. You have to describe
11 and enable, and they clearly did not do it.
12 Q I understand that's your opinion.
13 But I'm trying to understand
14 whether or not you -- it's your opinion that
15 it's -- it was not possible to achieve or
16 obtain the sequences of Limulus polyphemus
17 Factor C, Factor B and proclotting enzyme as of
18 December 2013?
19 MS. LOUGHRAN: Objection. Form.
20 A Based on the -- the wording that I
21 recited from paragraph 13, and considering that
22 they were working on elucidating the sequences
23 around 2014 time frame, it appears the
24 inventors did not.

1 But beyond that, I don't think I
2 can speculate on that.
3 Q So you don't have an opinion one way
4 or the other whether it was possible for a POSA
5 to obtain those sequences as of December 2013?
6 MS. LOUGHRAN: Objection. Form.
7 A So let me -- let me -- let's take a
8 step back. We keep talking about the
9 sequencing, but let's understand the workflow
10 for getting the sequence. And I talked about a
11 bit of it.
12 The first step for a POSA to
13 even start the work on getting the sequence is
14 to get hold of Limulus horseshoe crab blood or
15 amoebocytes.
16 If I'm sitting as a POSA, where
17 am I going to get the blood from? I'm not
18 going -- I can't go and catch a horseshoe crab.
19 It requires a permit. I need to have a
20 facility to bleed horseshoe crab. It's not
21 straightforward to have research
22 collaborations, I'm sure you're aware, with the
23 companies that do the bleeding.
24 So for a POSA, even starting to

1 get into the process of sequencing the Limulus
2 factors would be extremely difficult and a
3 nonstarter.
4 And after that, like I
5 mentioned, it comes down to what would be the
6 mRNA expression level. Then they could use --
7 like you said -- Dr. Frohman said, they could
8 have used RACE or something, then analyzing the
9 data to identify the variants, identify any
10 kind of paralogs, and then they would have
11 everything.
12 And each step has its own
13 challenges, even from the first step, which
14 could be a nonstarter for a POSA.
15 So not an ordinary POSA can just
16 go and get started on sequencing Limulus
17 Factor C.
18 Q So you're saying it's impossible?
19 MS. LOUGHRAN: Objection. Form.
20 A "Impossible" is probably a strong
21 word, but I would say it's certainly difficult
22 for a POSA who lacks the resources to even have
23 the starting point of horseshoe crab blood or
24 amoebocytes to be able to get started in the

1 process.
2 And you can see in the
3 specifications, in '498 and '629, they started
4 with blood. Ding for Carcinoscorpius started
5 with amoebocytes. And these are not stuff that
6 you can purchase from a vendor.
7 Q The Limulus lysate is available for
8 purchase, right?
9 A Okay. If Limulus -- I'll counter
10 that point. But if Limulus lysate was that
11 simple to use -- get the mRNA, why didn't any
12 of the inventors not start with that?
13 There's a reason everyone is
14 starting with blood, and the reason is that if
15 even you use simply lysate, the RNases are
16 likely to have already chopped the RNA that is
17 present.
18 And that is the reason why if
19 you look at '498 PCT or '629 specification,
20 they take the blood and use TRIZol, which
21 includes guanidine isothiocyanate to inhibit
22 RNases.
23 Likewise, when Ding did it, they
24 took amoebocytes and they added guanidine

1 isothiocyanate directly, and this is
2 specifically to inhibit RNases so that the mRNA
3 is not chopped, degraded and they can start the
4 process.
5 So no, lysate would not be a
6 starting point. By then, when you get to
7 lysate, likely the mRNA is not even available
8 or usable.
9 Q So you disagree -- so you recall the
10 Frohman declaration, correct?
11 A Yeah, we talked about it.
12 Q So you disagree with Dr. Frohman in
13 terms of the ability to obtain the cDNA
14 sequence of Limulus Factor C?
15 A No, I didn't say --
16 MS. LOUGHRAN: Objection. Form.
17 A I didn't say I'm disagreeing. And I
18 used these words before also. His opinion is
19 on one element of the whole workflow of getting
20 the cDNA sequence of Limulus Factor C. He is
21 focused on the sequencing aspect.
22 If I'm a POSA, I'm thinking, for
23 the end-to-end workflow of how I'm going to
24 start with the starting raw material, which is

1 the horseshoe crab blood, and then get through
2 mRNA and then sequencing, which is what
3 Dr. Frohman talks about, and then be able to
4 analyze the data.
5 And he's giving his theoretical
6 opinion. I'm giving my opinion based on my
7 assessment of the whole workflow. He gave his
8 opinion based on his area, which is around the
9 sequencing.
10 So there's no question about
11 disagreeing with him. We are speaking from
12 different perspectives.
13 And I don't believe in any of my
14 testimony so far I've claimed to be disagreeing
15 with him on the sequencing aspect.
16 I mean, I have to think about
17 the whole end-to-end workflow.
18 Q Do you recall from the Frohman
19 declaration that he opined that someone working
20 in the field could obtain the Limulus Factor C
21 sequence within a matter of days?
22 A Yeah, I recall. Somewhere in this
23 stack, I don't have it in front of me, but I
24 recall he said something.

1 But, like I said, he's speaking
2 more from sequencing aspect.
3 Q Sure.
4 But you also opined that after
5 you obtained the sequence, then a POSA would
6 have reasonably expected Limulus polyphemus
7 Factor C expressed in HEK293 cells to exhibit
8 similar values of residual activity as those
9 reported for T. tridentatus, correct?
10 MS. LOUGHRAN: Objection. Form.
11 A So we're talking about different
12 things. He's talking about being able to
13 obtain the sequence. You are talking about my
14 declaration on being able to express the
15 protein and get the residual activity.
16 Q No, you just told me that it's -- it
17 would be nearly impossible for a POSA to
18 actually obtain the cDNA sequence of Limulus
19 polyphemus Factor C as of December 2013.
20 MS. LOUGHRAN: Objection.
21 Argumentative.
22 A Yes. And we have different starting
23 points.
24 For sequence you need to start

1 with horseshoe crab blood. I'm speaking that
2 if the sequence is available -- if and when the
3 sequence is available, the starting points are
4 different.
5 So I'm not starting from
6 horseshoe crab blood. I'm starting from a
7 published sequence. So we are actually
8 talking, like, what is it, apples and oranges
9 kind of situation.
10 THE DEPONENT: What time is it?
11 BY MS. LO:
12 Q So if a POSA didn't have to start
13 from horseshoe crab blood, then you would agree
14 that it would be possible to obtain the Limulus
15 polyphemus Factor C cDNA sequence as of
16 December 2013?
17 MS. LOUGHRAN: Objection. Form.
18 A Like I said, there could be
19 challenges based on mRNA quality and quantity
20 and analysis of variants and paralogs.
21 But if you're asking me to
22 speculate, then conceptually, yes, but not
23 without overcoming those challenges.
24 Q And once that sequence in hand, then

1 a POSA would have reasonably expected the
2 resulting Factor C protein to have residual
3 activity similar to the T. tridentatus Factor C
4 protein?
5 MS. LOUGHRAN: Objection. Form.
6 A Based on my analysis of '498 PCT and
7 '629 specification sequence.
8 But I think we're also -- from
9 what I'm understanding where you're going, I
10 think we are also now expecting a POSA to take
11 on this extra work of getting the sequence and
12 then using -- replicating the -- the invention
13 by -- of '767 application, and then giving the
14 credit of all of that to the inventors, when
15 the POSA would have done a pretty significant
16 amount of work.
17 It's a little bit of an unfair
18 situation towards the POSA.
19 Should we take a break?
20 MS. LOUGHRAN: Yeah, we've been
21 going about an hour or so.
22 MS. LO: Yeah, we can take a
23 break.
24 (Recess.)

1 BY MS. LO:
2 Q So, Dr. Jain, before the break, we
3 were talking about difficulties that you
4 identified that a POSA might encounter in
5 obtaining the cDNA sequence of Factor C.
6 I -- can you confirm that you
7 hold the same opinions with respect to the
8 ability of a POSA to obtain the sequences of
9 Limulus polyphemus Factor B and proclotting
10 enzyme as of December 2013?
11 A Yes, I do. They would be coming out
12 of the same horseshoe crab blood and would have
13 the same challenges of variants.
14 We know that, from '629
15 specification, that proclotting enzyme had I
16 believe five variants.
17 Q So with respect to the '629
18 publication, is it your opinion that the work
19 described in the '629 publication or cloning
20 the cDNA of the polyphemus Factor C involves
21 undue experimentation?
22 MS. LOUGHRAN: Objection. Form.
23 A So the inventors have primarily
24 talked about the sequencing steps involved

1 in -- from horseshoe crab blood to getting the
2 cDNA sequence. I do find that they have --
3 they had to encounter challenges in the
4 process, and that required them to take
5 additional steps.
6 So it was certainly difficult --
7 a difficult process. Hard for me to say if it
8 was undue experimentation or not, but it was
9 certainly a difficult process.
10 Q But it's your opinion that the '629
11 publication is enabled, correct?
12 MS. LOUGHRAN: Objection. Form.
13 A '629 publication is enabled for '109
14 or --
15 Q Well, it's --
16 A Because there it is anticipated.
17 It's not describing the full claim -- full
18 scope of the claim.
19 Q Sure. It might help if you looked at
20 your PGR declaration, Exhibit 2 --
21 A Okay.
22 Q -- paragraph 1 -- starting at
23 paragraph 188.
24 A 188, okay.

1 (The deponent read the
2 document.)
3 A Yes.
4 Q And so in paragraphs 188 through 193,
5 you're expressing the basis for your opinion
6 that the '629 publication is enabled, correct?
7 A So when you look at the last sentence
8 under paragraph 188, what it says is that it is
9 enabled for the purposes of anticipating the
10 challenged claims of '109 patent.
11 So in my understanding, not
12 being a lawyer, but from my understanding, as
13 I've been explained, is that anticipation means
14 that one -- one example within the full scope
15 of the claim has been enabled or has been
16 demonstrated.
17 So from that perspective of
18 anticipation, yes, '629 enables that
19 anticipation by showing one example out of
20 3,400-something combinations of claim 1 of '109
21 specification.
22 Q Okay.
23 And so in paragraph 190, you
24 state that POSAs did carry out the directives

1 provided in the '629 publication without undue
2 experimentation, correct?
3 A Just a second.
4 MS. LOUGHRAN: Objection. Form.
5 (The deponent read the
6 document.)
7 A Yes. So if a POSA now has the
8 sequence of Limulus Factor C, Factor B and
9 proclotting enzyme, and now they are looking to
10 express and put them together as per claim 1 of
11 '109, then yes, I agree that for that one
12 example, it's not -- there's no instance of
13 undue experimentation.
14 Q And the disclosure and examples of
15 the '629 publication also includes obtaining
16 Limulus amoebocyte lysate --
17 A Reverse --
18 Q Reverse, yes.
19 MS. LOUGHRAN: Objection. Form.
20 Q And RT-PCRing and cloning it out,
21 correct?
22 MS. LOUGHRAN: Objection. Form.
23 A That is correct.
24 Q And obtaining the cDNA sequence of

1 Limulus polyphemus Factor C, Factor B and
2 proclotting enzyme and expressing them in
3 mammalian cells was not undue experimentation
4 according to paragraph 190 of your PGR
5 declaration.
6 MS. LOUGHRAN: Objection. Form.
7 Mischaracterizes testimony.
8 A So paragraph 190 talks about once we
9 have the sequence available, then the element
10 of expressing those three proteins and putting
11 them together. It's not talking about
12 generating the sequence -- determining the
13 sequence of the three proteins, because that is
14 not a requirement within claim 1.
15 Claim 1 talks about expressing,
16 putting together the cascade, and showing
17 function. So from that view of claim 1 of
18 '109, the aspects of '629 that are applicable
19 are not the sequencing but rather, once the
20 sequence is available, expression and putting
21 together the cascade.
22 Because it says claimed methods.
23 Claimed method is claim -- claims 1 to 9. It's
24 not the claimed methods of '629. It's the

1 claimed methods of -- for '109 claim 1.
2 Q Right.
3 And so the -- everything
4 downstream of obtaining the sequences was not
5 undue experimentation for a POSA?
6 MS. LOUGHRAN: Objection. Form.
7 A I would consider that. Of course
8 because the '629 specification showed examples
9 of expressing Limulus factors in CHO cells, so
10 I don't consider that aspect to be undue
11 experimentation. Specifically that part.
12 Q So for a POSA, following the examples
13 in the '629 publication was not undue
14 experimentation?
15 MS. LOUGHRAN: Objection. Form.
16 Asked and answered.
17 A Specifically related to replicating
18 protein expression and putting together the
19 cascade for those elements, yes.
20 Q We've been talking about the '629
21 publication and the '498 PCT.
22 Would you agree that those two
23 documents contain substantially the similar
24 disclosures as far as like the patent

1 specification is concerned?
2 A That is correct.
3 Q Okay. All right.
4 If you can turn to Exhibit 1,
5 your IPR declaration.
6 A Okay.
7 Q I'll direct your attention to
8 paragraph 112.
9 A Okay.
10 Q Okay.
11 And here you're quoting from the
12 '498 publication, correct?
13 A That is correct.
14 Q How do these quoted statements
15 evidence a struggle in accomplishing the
16 recombinant production of Limulus polyphemus
17 proteins?
18 MS. LOUGHRAN: Objection. Form.
19 A Sorry, I'm not sure if I understood
20 the question, if you could just clarify.
21 Q Sure.
22 So you state kind of in the
23 middle/upper third, "In this PCT, the inventors
24 detailed the struggle the field encountered in

1 accomplishing the recombinant production of
2 Limulus polyphemus proteins."
3 Then you quote some -- you have
4 a quote and then cite some paragraphs.
5 And my question is, how did
6 these statements about no lack of reports
7 evidence a struggle in the field?
8 A So just give me a moment, because I'm
9 going to go to the specification.
10 (The deponent read the
11 document.)
12 A So this is basically looking at the
13 whole set of paragraphs that provide the
14 context behind this sentence. And if I quote
15 from -- from paragraph 12 of PCT or '629, it
16 goes to say that this is because -- "complete
17 identification of these proteins and genes from
18 both structure and functional aspects has not
19 been achieved, even though 20 years or more has
20 passed since the reports regarding the genus
21 Tachypleus described above were published."
22 "This is because accurate
23 determination of the full-length sequence
24 structures and elucidation of the expression

1 and functions of these proteins and genes could
2 not be achieved by general techniques."
3 And we talked about this
4 earlier.
5 So it's -- even though you see
6 one sentence quoted, it was that whole context
7 of information in the subsequent paragraphs
8 that highlighted the challenges that are
9 associated or were associated with determining
10 the sequences for Limulus factors.
11 Q So you're not relying on the lack of
12 reports to conclude there is a struggle in the
13 field?
14 A Lack of report is more of an outcome
15 of the challenges and the challenge was
16 highlighted in -- I think I said paragraph 13.
17 So it was basically that whole block of
18 content -- yeah, content or text.
19 Q When you prepared your declarations,
20 were you aware of publications discussing the
21 extent of homology between Limulus polyphemus
22 Factor C and the Factor C of other crab
23 species?
24 A I had seen some publications, but

1 also I became aware of the '432 patent that you
2 had referenced in response to my declaration.
3 Q And do you recall -- but you didn't
4 come across that reference prior to submitting
5 your declaration?
6 A No, I had not seen that at the time
7 of my declaration.
8 Q And that was even though you surveyed
9 the literature and searched Google patents and
10 all that, Google Scholar, et cetera?
11 A Yes, but it is -- it happens when
12 you're doing the research that depending on the
13 keywords that we use and how we are searching,
14 we find some, we -- there can be an occasional
15 miss.
16 Q Okay.
17 And there is also another
18 reference published in 2006 by Alwis and Milton
19 that referenced the extent of homology between
20 Limulus polyphemus Factor C and the Factor C of
21 other species?
22 A So I don't recall them mentioning or
23 discussing homology. I recall they're
24 discussing similarity between LAL and

1 recombinant Factor C, which was
2 Carcinoscorpius.
3 And if you look at the data,
4 they found that LAL led to twice as much
5 endotoxin value as the recombinant Factor C.
6 They did not discuss why, but
7 they saw that there is a correlation between --
8 or they are correlated. The value that they
9 got from LAL and the value they got from rFC
10 are correlated, but there was -- there was a
11 difference in values.
12 LAL was giving twice as much
13 value, which could have been for different
14 reasons, including different degree of
15 sensitivity of each Factor C to the type of
16 endotoxin.
17 Q But the overall conclusion in that
18 2006 paper was that the LAL and the recombinant
19 Factor C assay gave comparable results,
20 correct?
21 MS. LOUGHRAN: Objection. Form.
22 A So when -- when we -- as a POSA when
23 we review general publications -- and there's a
24 reason why publications include data -- is that

1 we don't just look at the conclusions made by
2 the authors, because they may be looking at
3 data from a certain perspective. And in their
4 case, they were likely looking for a
5 correlation between LAL and rFC.
6 On the other hand, when I looked
7 at the data, it was very clear throughout the
8 paper that they were getting twice the value of
9 endotoxin than they were -- with the LAL
10 reagent than they were getting with rFC.
11 So if you're looking at them to
12 be comparable in the sense that they're going
13 to behave similarly, then the answer is no.
14 If you look at it from their
15 perspective that they were trying to claim that
16 rFC could be a replacement for LAL because the
17 values are correlated, then for their
18 application, the answer is yes. It comes down
19 to all context, and authors write --
20 researchers write papers and they have some
21 idea in their mind. They draw conclusions
22 based on that. They interpret data in that
23 way.
24 But it's for scientists and

1 POSAs like myself to understand the data
2 broader than the statements and opinions made
3 by the researchers.
4 MS. LO: Let's go ahead and mark
5 as Exhibit --
6 A 9.
7 Q -- 9 -- thank you -- the '432
8 publication that you referenced.
9 (Exhibit 9 marked for
10 identification.)
11 BY MS. LO:
12 Q So we're going to hand you Exhibit 9,
13 which is US 2003/0054432.
14 A Thank you.
15 Q Dr. Jain, just if you can confirm,
16 this was the '432 publication that you
17 referenced a few answers ago?
18 A That is correct.
19 Q And in Example 11, which is on
20 page 21 --
21 A Page 21. Page 21 of the bottom
22 marking or the top marking?
23 Q The bottom marking.
24 A Okay.

1 Q And in Example 11, it discusses
2 tryptic peptide sequencing.
3 A Yes.
4 Q And what is tryptic peptide
5 sequencing?
6 A So tryptic peptide sequencing is
7 where -- it's used for -- typically for
8 fingerprinting. A protein is digested using
9 trypsin enzyme, which cleans the proteins at
10 specific spots. It generates the peptides, and
11 those peptides are then sequenced to see like a
12 fingerprint of the protein. It's not a
13 complete sequence. It's a fingerprint.
14 And just to put it in
15 perspective, when Muta generated cDNA sequence
16 and they wanted to confirm the sequence, they
17 did tryptic mapping. And the sequence that
18 they got combined with the sequence that they
19 said was known, they got a little less than
20 50 percent of the sequence of the full protein.
21 So, like I said, it's a
22 fingerprint for a protein. I'm going to stop
23 there.
24 Q Have you ever conducted tryptic

1 peptide sequencing?
2 A Not personally. But when we make
3 recombinant protein drugs for identification
4 purposes, the tryptic mapping is one of the
5 tools that is used to confirm that the correct
6 protein was expressed.
7 Q And how much protein do you need to
8 conduct this -- this method?
9 A It's -- I can speak from some of my
10 conversations when I had to get it -- request
11 it or get it done.
12 It's typically on the order
13 of -- in the milligram range, so, like, maybe
14 10 milligram. Something like that. Not like
15 grams but not micrograms either.
16 Q Okay.
17 That's a lot more than --
18 withdrawn.
19 After you obtain the amino acid
20 sequence, even if it's partial, of a protein by
21 tryptic peptide sequencing, it's possible to
22 predict the cDNA sequences to some degree,
23 correct?
24 MS. LOUGHRAN: Objection. Form.

1 A I would say possibly, but it would be
2 partial.
3 Like I said, Muta could not --
4 got less than 50 percent after tryptic mapping
5 and the sequence that was known in the -- in
6 the literature or in the history. So tryptic
7 mapping alone gave even less of the sequence.
8 So yes, it could be a partial,
9 but significantly partial sequence, I would
10 think. And this is the pattern like where I
11 also reference the aspect that the inhibition
12 enhancement profile of Limulus was different
13 than for Carcinoscorpius, which is actually
14 just two paragraphs before in 132.
15 So just mentioning that I
16 mentioned it at some point previously.
17 Q So does the ability of the inventors
18 on this '432 publication to obtain milligrams
19 of Factor C protein affect your opinions
20 expressed earlier that it would have been
21 nearly impossible for a POSA to obtain enough
22 amoebocyte lysate to obtain an mRNA sample of
23 it?
24 MS. LOUGHRAN: Objection. Form.

1 A So first of all -- and I have to
2 again recheck, but if you allow me to check
3 that, I can check that.
4 (The deponent read the
5 document.)
6 A I don't see it, but my recollection
7 is the way they got Limulus Factor C was by --
8 actually, it does say here, sorry. In 134,
9 first sentence. "We isolated the Factor C from
10 Limulus," and then they talked about "generated
11 antisera" and everything.
12 So this Limulus Factor C was not
13 recombinant. It was purified from lysate. But
14 because now you're looking at protein, not mRNA
15 for sequencing, they could have started with
16 lysate, which is a completely different
17 situation than getting the mRNA and cDNA in
18 sequence.
19 Q I see. Okay.
20 A Sometimes things are in front of you
21 and you don't find it.
22 Q I'm sorry?
23 A I'm saying sometimes things are in
24 front of you, the sentence, and you don't find

1 it.
2 MS. LO: All right. Can we go
3 off the record?
4 (Discussion off the record.)
5 MS. LO: I pass the witness.
6 MS. LOUGHRAN: Are you passing
7 as to both cases?
8 MS. LO: I am, yes.
9 MS. LOUGHRAN: Okay. Can we
10 just take a -- one quick break? I just --
11 sorry, I just want -- I didn't know if you had
12 any other questions. We'll just go off the
13 record one more time and then we'll come back
14 if I have any redirect.
15 (Discussion off the record.)
16 (Recess.)
17
18 EXAMINATION
19 BY MS. LOUGHRAN:
20 Q Good afternoon, Dr. Jain.
21 How are you?
22 A I'm okay.
23 Q Okay.
24 I'd like you to go back to

1 Exhibit 4, the Frohman declaration that counsel
2 was asking you about earlier.
3 A Okay.
4 Q Do you have that?
5 A Yes.
6 Q And you reviewed this declaration?
7 A I did.
8 Q Does Dr. Frohman make any statements
9 or draw any conclusions or opinions about
10 written description or enablement for the full
11 scope of claim 21 of the '318 patent?
12 MS. LO: Objection to form.
13 A He did not.
14 Q Okay.
15 Does Dr. Frohman make any
16 statements or draw any conclusions or opinions
17 about written description or enablement for the
18 full scope of claims 1 through 9 of the '109
19 patent?
20 MS. LO: Objection to form.
21 A He did not.
22 Q Okay.
23 Did anything in the Frohman
24 declaration change any of the opinions that you

1 provided in your declaration?
2 A They did not.
3 Q Okay.
4 And if you just want to pull up
5 the '432 publication, I think it was marked --
6 A The last one?
7 Q Yeah, the last one. I think maybe
8 Exhibit 9.
9 A Okay.
10 Q I think that you testified that you
11 became aware of this publication because you
12 saw it cited in patent owner's preliminary
13 response; is that correct?
14 A That is correct, in the response
15 issued in June.
16 Q Yes, okay.
17 Having reviewed this subsequent,
18 does anything in Exhibit 9 change any of the
19 opinions in either of your declarations
20 discussed today?
21 A No, it does not change. And rather,
22 it further validated the differences between
23 Tachypleus and Limulus Factor C based on the
24 information in paragraph 132 where they said,

1 "The enhancing/inhibiting effect of Zwittergent
2 3-14," it's a component, "was also tested using
3 purified Limulus Factor C (Figure 6). A
4 similar enhancing/inhibiting effect was
5 observed, although" -- and this is important --
6 "the relative Factor C activity ratio and
7 enhancing and inhibiting detergent
8 concentrations were different from those in the
9 recombinant Factor C assay."
10 So it further supported my
11 argument.
12 MS. LOUGHRAN: I have no further
13 questions for Dr. Jain in either case.
14 MS. LO: Thank you. Nothing
15 further. Thank you for your time.
16 THE DEPONENT: Thank you.
17 (Whereupon, the proceedings
18 adjourned at 4:27 p.m.)
19
20
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24

1 C E R T I F I C A T E

2 I, Jill K. Ruggieri, Registered Merit
3 Reporter and Certified Realtime Reporter, do certify
4 that the deposition of SIDDHARTHA JAIN, PhD, in
5 the above-captioned matter, on November 4, 2025, was
6 stenographically recorded by me; that the witness
7 provided satisfactory evidence of identification, as
8 prescribed by Executive Order 455 (03-13) issued by
9 the Governor of the Commonwealth of Massachusetts,
10 before being sworn by me, a Notary Public in and for
11 the Commonwealth of Massachusetts; that the
12 transcript produced by me is a true record and
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14 ability; that I am neither counsel for, related to,
15 nor employed by any of the parties to the above
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17 employee of any attorney or counsel employed by the
18 parties thereto, nor financially or otherwise
19 interested in the outcome of the action.
20
21
22 Jill K. Ruggieri, RPR, RMR, FCRR, CRR
23
24 Transcript review was requested of the reporter.

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November 14, 2025
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To: Ms. Loughran
6

Case Name: Charles River Laboratories, Inc. v. Seikagaku Corporation
7

Veritext Reference Number: 7681195
8

Witness: Siddhartha Jain , PhD Deposition Date: 11/4/2025
9

10 Dear Sir/Madam:
11

Enclosed please find a deposition transcript. Please have the witness
12

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1 DEPOSITION REVIEW
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2
ASSIGNMENT REFERENCE NO: 7681195
3 CASE NAME: Charles River Laboratories, Inc. v. Seikagaku Corporation
DATE OF DEPOSITION: 11/4/2025
4 WITNESS' NAME: Siddhartha Jain , PhD
5 In accordance with the Rules of Civil Procedure, I have read the entire transcript of
6 my testimony or it has been read to me.
7 I have made no changes to the testimony as transcribed by the court reporter.
8
_____ _____
9 Date Siddhartha Jain , PhD
10 Sworn to and subscribed before me, a Notary Public in and for the State and County,
11 the referenced witness did personally appear and acknowledge that:
12
They have read the transcript;
13 They signed the foregoing Sworn Statement; and
14 Their execution of this Statement is of their free act and deed.
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1 DEPOSITION REVIEW
CERTIFICATION OF WITNESS
2
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DATE OF DEPOSITION: 11/4/2025
4 WITNESS' NAME: Siddhartha Jain , PhD
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7 I have listed my changes on the attached Errata Sheet, listing page and line numbers as
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