

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHARLES RIVER LABORATORIES,)
INC.,)
)
Petitioner,)
)
vs.) Case No. IPR2025-00440
) Patent No. 11,236,318
SEIKAGAKU CORPORATION,)
)
Patent Owner.)

DEPOSITION OF BRIAN SCHAEFER, Ph.D.
TAKEN ON BEHALF OF PETITIONER
FEBRUARY 12, 2026

VOLUME 1

Reported by Celena D. Davis, RPR, CSR

CRL Exhibit 1067
CRL v. Seikagaku
IPR2025-00440

1	INDEX OF EXAMINERS		
2	DEPOSITION OF BRIAN SCHAEFER, Ph.D.		
3			Page:
4	Questions by Ms. Loughran	5	
5	EXHIBITS		
6	Exhibit 1001	39	
	(US Patent No. 11,236,318)		
7	Exhibit 1005	177	
	(498 PCT)		
8	Exhibit 1006	43	
	('767 Patent Application)		
9	Exhibit 1007	190	
	(Muta publication)		
10	Exhibit 1016	190	
	(Iwanaga article - 2007)		
11	Exhibit 1022	131	
	(Tokunaga 1991 reference)		
12	Exhibit 1066	70	
	("Genomic Surveillance of Rabies Virus"		
13	article)		
	Exhibit 2035	149	
14	(Chen, et al. US Patent Application)		
	Exhibit 2036	156	
15	(Alwis article)		
	Exhibit 2038	13	
16	(Declaration of Brian Schaefer, Ph.D.)		
	Exhibit 2044	66	
17	(Obst article)		
	Exhibit 2049	168	
18	(Loverock article)		
	Exhibit 2053	95	
19	(Alwis article)		
	Exhibit 2062	15	
20	(Declaration of Brian Schaefer, Ph.D.)		
	Exhibit 2062 (duplicate exhibit numbers)	86	
21	(Bolden article)		
	Exhibit 2075	179	
22	(Thorne article)		
	Exhibit 2081	111	
23	(Clustal O(1.2.4) Sequence)		
	Exhibit 2100	124	
24	(Phyre 2.2 Results for Factor C)		
25	(The exhibits are attached.)		

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7) Patent No. 11,236,318
SEIKAGAKU CORPORATION,)
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Patent Owner.)

9
10 IT IS STIPULATED AND AGREED by and between
11 counsel for Petitioner and counsel for Patent Owner that
12 the deposition of BRIAN SCHAEFER, Ph.D. may be taken for
13 Discovery purposes by and on behalf of the Petitioner,
14 pursuant to the provisions of the rules pertaining to
15 depositions taken for the Petitioner on February 12,
16 2026, at the law offices of Morgan, Lewis & Bockius, 110
17 N. Wacker Drive, in the City of Chicago, State of
18 Illinois, before CELENA D. DAVIS, Registered
19 Professional Reporter and Certified Shorthand Reporter
20 within and for the State of Illinois.

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APPEARANCES

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CERTIFIED LIVENOTE REPORTER
MAGNA LEGAL SERVICES
Celena D. Davis

1 (The deposition began at 9:02 a.m. CST.)

2 BRIAN SCHAEFER, Ph.D.,
3 duly sworn to tell the truth, the whole truth, and
4 nothing but the truth, testified as follows:

5 EXAMINATION

6 QUESTIONS BY MS. LOUGHRAN:

7 Q. Good morning, Dr. Schaefer. How are you
8 today?

9 A. I'm good. How are you?

10 Q. Good. My name is Chelsea Loughran. I'm an
11 attorney from the firm Wolf, Greenfield & Sacks. I
12 represent the petitioner in this matter, Charles River
13 Laboratories. And with me here today is my colleague,
14 also from the same firm. Her name is Flora Luo.

15 Could you just spell and state your name
16 for the record, please?

17 A. Brian Schaefer. That's Brian with an I,
18 B-R-I-A-N, Schaefer, S-C-H-A-E-F-E-R.

19 Q. And where do you currently live, sir?

20 A. I live in Maryland.

21 Q. And are you represented by counsel today?

22 A. Counsel is here with we me today, yes.

23 Q. Is that Shon Lo from Morgan Lewis?

24 A. Yes, it is.

25 Q. You understand that you've been placed

1 under oath; correct?

2 A. I understand.

3 Q. You understand that you're required to
4 testify truthfully today; right?

5 A. I understand.

6 Q. Is there any reason you can't give true and
7 accurate testimony today?

8 A. No reason whatsoever.

9 Q. Okay. And have you ever testified in a
10 deposition before?

11 A. There was probably a deposition associated
12 with my divorce, but I'm not 100 percent sure of that.
13 It was a little while ago.

14 Q. Okay. So never a deposition in relation to
15 a patent case, for example?

16 A. Correct.

17 Q. And since that may have been a while ago,
18 I'm just going to lay a couple of ground rules just so
19 we're operating on the same page today.

20 I'm going to ask you a series of questions
21 today about some testimony that you submitted in
22 connection with two matters between my client, Charles
23 River Laboratories, and the patent owner in this matter,
24 Seikagaku.

25 I'm just going to ask that you answer all

1 of my questions to the best of your ability; okay?

2 A. Yes.

3 Q. All right. Now, at any point if you don't
4 understand one of my questions, you are free to ask me
5 to rephrase it or tell me that you don't understand.
6 But if you answer the question, I'm going to assume that
7 you understood my question.

8 Do you understand?

9 A. Understood.

10 Q. Okay. We'll take breaks during the
11 deposition around every hour just to give the court
12 reporter here a little break and everybody a break. If
13 you need a break before that, just let me know.

14 The one caveat to that is that if there is
15 a pending question, I will require you to answer the
16 question before we break.

17 Do you understand?

18 A. I understand.

19 Q. You do have to answer all my questions
20 unless your counsel, Ms. Lo, instructs you specifically
21 not to answer.

22 I may ask you a question; she may object to
23 the question; you still have to answer that question
24 unless she tells you specifically do not answer that
25 question; okay?

1 A. Understood.

2 Q. And as you see, we are hopefully joined by
3 a court reporter here today who's transcribing all of
4 your testimony, so I will ask that all of your answers
5 to my questions are verbal. Shrugs or nods can't be
6 recorded by the court reporter, so we're going to do all
7 of this with verbal questions and answers; okay?

8 A. Understood.

9 Q. Great.

10 So, Dr. Schaefer, you have been retained by
11 the patent owner in this matter, Seikagaku Corporation;
12 correct?

13 A. That's correct.

14 Q. All right. How did you come to be involved
15 in the -- two matters, actually. There's an IPR related
16 to a patent that ends in 318. I'll call that the IPR.
17 And then there's a PGR that relates to a patent that
18 ends in 109. I'll call that the PGR.

19 How did you come to be involved in the IPR
20 and the PGR?

21 MS. LO: I will just interpose a caution to
22 Dr. Schaefer not to divulge the substance of any
23 discussion he may have had with counsel.

24 THE WITNESS: Understood.

25 A. I was approached by Shon Lo based on my

1 expertise. We had a conversation and I agreed to
2 participate.

3 BY MS. LOUGHRAN:

4 Q. Okay. When, approximately, was -- were you
5 approached by Ms. Lo?

6 A. Last year, I believe, before midyear. But
7 I really don't have specific recollection of the date,
8 even the month.

9 Q. Okay. And prior to being approached by
10 Ms. Lo, did you have any relationship with the patent
11 owner in this case, Seikagaku, before that in terms of
12 being a consultant or employee of that entity?

13 A. No, no relationship.

14 Q. Had you ever heard of Seikagaku before
15 being approached by Ms. Lo?

16 A. Not to my knowledge. Many of these
17 Japanese companies have similar sounding names, so I
18 couldn't say for sure, but it was not familiar to me.

19 Q. Okay. Had you heard of the petitioner in
20 this matter, Charles River Laboratories, before being
21 approached about these cases?

22 A. I'm familiar with the petitioner.

23 Q. I do want you to just wait until I'm
24 finished answering [sic] my question before you answer
25 it because, again, the court reporter can't transcribe

1 us speaking at the same time.

2 A. I will do my best.

3 Q. It does get stilted, but I will ask that
4 you wait.

5 And so you said you do remember Petitioner
6 Charles River.

7 What have been your interactions with
8 Charles River before being involved in these cases?

9 A. Charles River Laboratories is one of the
10 big vendors for laboratory mice. My laboratory works
11 quite a bit with laboratory mice, so I'm familiar with
12 the major vendors.

13 Q. Okay. So have you purchased lab mice from
14 Charles River?

15 A. Charles River is actually a company where
16 we have our breeding colony based on an agreement
17 between my university and Charles River to supply those
18 services.

19 Q. Okay. And what is your university?

20 A. Uniformed Services University.

21 Q. Okay. And other than purchasing or
22 breeding mice at Charles River, have you ever done any
23 consulting or worked for Charles River?

24 A. No, never anything like that.

25 Q. Okay. You're aware that there are other

1 experts who are involved in these matters; right?

2 A. I am aware of that.

3 Q. Okay. And I think in your declaration,
4 which we'll get to, you reference an individual by the
5 name of Dr. Tina Morris; is that correct?

6 A. That is correct.

7 Q. Had you ever heard of or did you know
8 Dr. Morris before being involved in these cases?

9 A. I have never met Dr. Morris. I was not
10 familiar with her.

11 Q. Have you spoken with Dr. Morris in the
12 course of your consulting for these cases?

13 A. I have not spoken to Dr. Morris.

14 Q. I think you said you read her declaration;
15 is that correct?

16 A. Yes, I read her declaration.

17 Q. Other than reading her declaration, have
18 you had any interaction with Dr. Morris?

19 A. None whatsoever.

20 Q. Did you read the transcript of her
21 deposition testimony?

22 A. I don't believe I read that, no.

23 Q. Are you aware there's an expert in this
24 case by the name of Dr. Siddhartha Jain?

25 A. Yes, I'm aware.

1 Q. Did you have any awareness of Dr. Jain
2 before being involved in these matters?

3 A. No, I did not.

4 Q. Have you ever spoken with Dr. Jain before
5 being involved in these cases?

6 A. Not to my knowledge.

7 Q. I think you indicated that you read his
8 declarations and his deposition testimony; is that
9 correct?

10 A. Yes, I read those.

11 Q. Okay. Dr. Schaefer, in the course of your
12 preparation and the forming of your opinions in this
13 case, have you spoken with anybody at Seikagaku
14 Corporation?

15 A. No.

16 Q. Have you had any interactions with the
17 inventors on the '318 or '109 patents?

18 A. None whatsoever.

19 Q. Had you had any interactions with those
20 inventors prior to being involved in these matters?

21 A. Not that I'm aware of.

22 Q. All right. I think at this point, I would
23 like to introduce the testimony that you have provided,
24 so your two declarations in these cases.

25 I will hand you -- the first one has been

1 marked -- premarked Exhibit 2038. There's a declaration
2 of Brian C. Schaefer, Ph.D., in Case Number
3 IPR2025-00440, Patent No. 11,236,318.

4 All right. Dr. Schaefer, I've handed you a
5 document that's marked Exhibit 2038 in the IPR.

6 Is this your declaration?

7 A. It does appear to be.

8 (Exhibit 2038 was shown to the witness.)

9 BY MS. LOUGHRAN:

10 Q. Okay. And at the end of -- if you turn to
11 the last page of this -- this document, it says it's
12 dated December 1, 2025 and it has a signature.

13 Is that your signature?

14 A. That is my signature.

15 Q. Okay. And did you sign this document?

16 A. I did.

17 Q. Okay. You signed it after reviewing it?

18 A. Yes.

19 Q. Okay. And did you verify the accuracy of
20 all the statements herein?

21 A. I did.

22 Q. Is there anything about this document that
23 you want to change as you sit here today?

24 A. Not that I'm aware of.

25 Q. Okay. Who wrote this document?

1 A. The document was written collaboratively
2 between myself and lawyers at Morgan Lewis.

3 Q. When you say "collaboratively," what do you
4 mean?

5 A. We each wrote parts of the declaration. We
6 each edited each other's work. It was a close
7 collaboration.

8 Q. And other than yourself, were there any
9 other individuals helping you or assisting you in
10 putting this declaration together?

11 A. None.

12 Q. So you don't have any assistants or
13 students who were working with you?

14 A. I would consider that unethical.

15 Q. Okay. At paragraph 1 of this declaration,
16 you say you're being compensated at your standard hourly
17 rate.

18 What is that?

19 A. \$800 an hour.

20 Q. I'm going to hand you the next exhibit, and
21 this has been marked PGR Exhibit 2062. It's the
22 declaration of Brian C. Schaefer, Ph.D., in Case Number
23 PGR2025-00023 relating to Patent No. 11,959,109.

24 (Exhibit 2062 was shown to the witness.)

25 BY MS. LOUGHRAN:

1 Q. Dr. Schaefer, in front of you, you have an
2 exhibit premarked Exhibit 2038 in the PGR.

3 Do you recognize this document?

4 A. I do.

5 Q. And what is it?

6 A. It is my declaration regarding the PGR.

7 Q. Okay. And if you look at the last page of
8 this document, you'll see there is a signature and a
9 date, December 1, 2025.

10 Is that your signature?

11 A. It is.

12 Q. And you did, in fact, sign this on
13 December 1, 2025?

14 A. I did.

15 Q. Did you review it before signing?

16 A. I did.

17 Q. Okay. And did you confirm that the
18 contents of this declaration are true and accurate to
19 the best of your ability?

20 A. I did.

21 Q. Sitting here today, is there anything you
22 want to change about this declaration?

23 A. Nothing that I'm aware of.

24 Q. All right. If you look at your IPR
25 declaration, if you look at paragraph 8, you have a

1 section there that talks about the materials reviewed.

2 Do you see that?

3 A. I do.

4 Q. And it lists a number of documents that you
5 said you have reviewed in putting together this
6 declaration; right?

7 A. Correct.

8 Q. And did you, in fact, review all of those
9 documents?

10 A. Yes.

11 Q. And you're prepared to discuss them today?

12 A. I'm prepared to discuss them. I may want
13 to see them again to refresh my memory. But, yes, I'm
14 prepared to discuss them.

15 Q. Okay. Now, Dr. Schaefer, just so that
16 we're all on the same page, there's a bunch of
17 complicated -- fairly complicated Latin terms that we're
18 going to use during the deposition today.

19 Just for the court reporter's benefit, I
20 want to have a base understanding of what we're going to
21 refer to when we use those terms.

22 So the petitioner in this matter is Charles
23 River Laboratories, Inc. I'll probably refer to them as
24 "Charles River," but I'd ask that you understand I'm
25 referring to the petitioner; okay?

1 A. Yes.

2 Q. Likewise, the patent owner is Seikagaku
3 Corporation. When I refer to "Seikagaku," I'll be
4 referring to the patent owner in this case; okay?

5 A. Understood.

6 Q. There are three species of horseshoe crabs
7 that we'll be talking about mainly today: One is
8 *Limulus polyphemus*. When I refer to the "Limulus crab,"
9 I will be referring to *Limulus polyphemus*; okay?

10 A. Okay.

11 Q. Same, there will be the reference to the
12 Japanese species of horseshoe crab, *Tachypleus*
13 *tridentatus*. If I refer to a horseshoe crab by the name
14 of "Tachypleus," I'll be referring to that crab; okay?

15 A. Okay.

16 Q. Finally there is the horseshoe crab
17 *Carcinoscorpius rotundicauda*, which is the Singaporean
18 species, and if I use the phrase "*Carcinoscorpius* crab,"
19 I'll be referring to that one today; okay?

20 A. Okay.

21 Q. Could you please turn your IPR declaration
22 paragraph 2.

23 You indicated that you have a Ph.D. in
24 immunology that was granted in 1995.

25 Do you see that?

1 A. I see that.

2 Q. What was the particular focus of your Ph.D.
3 research?

4 A. So my Ph.D. research dealt primarily with
5 latency in an Epstein-Barr virus. And it was very much
6 a molecular-biology-focused thesis where the goal was to
7 determine a previously undetermined promoter for the
8 Epstein-Barr virus protein EBNA1.

9 And the reason for that was that it was
10 understood at the time that there was a poorly
11 characterized program of latency in Burkitt's lymphoma
12 cell lines that the assumption was this was also
13 relevant in --

14 (Reporter clarification.)

15 A. -- Burkitt's lymphoma tumors,
16 B-u-r-k-i-t-t, and that it may also be relevant in
17 normal human Epstein-Barr virus infections that are
18 latent.

19 So Epstein-Barr virus is a very large
20 virus. It has complex latency programs. The best
21 characterized one is called Latency III where all of the
22 different Epstein-Barr virus nuclear antigen, or EVNAs,
23 are produced.

24 In this other form of latency that was not
25 well understood, Latency I, the goal was to identify the

1 promoter. And I used RACE PCR to identify the end of
2 the EBNA1 transcript, and that gave us the location of
3 the promoter. And the other thing I did was
4 characterize that promoter and it's activity.

5 Q. Okay. Now, your research that related to
6 your Ph.D. did not involve any zymogen proteins in the
7 horseshoe crab coagulation cascade; right?

8 A. The horseshoe crab field is quite small. I
9 am not an investigator in that field. However, for the
10 purposes of offering opinions and expertise related to
11 the patents in question, what is really needed is a
12 solid foundation in molecular biology, particularly
13 regarding the question of when these sequences were
14 actually available to the inventors.

15 So I do not consider my lack of specific
16 work with horseshoe crabs as an impediment to offering
17 expert testimony.

18 Q. Okay. And I'm not suggesting it was. I
19 just wanted an answer to the question that your Ph.D.
20 research was not related to zymogen proteins from the
21 horseshoe crab; right?

22 A. I believe I answered the question with a
23 definitive answer that I did not work on horseshoe
24 crabs, but also that that type of expertise is not
25 necessary to answer the other questions that you're

1 going to be asking me.

2 Q. Okay. So you agree that you don't need to
3 work specifically with horseshoe crab zymogen proteins
4 to have the skill and expertise to provide relevant
5 testimony in this matter; right?

6 A. I consider the statement you just made
7 accurate; correct.

8 Q. Okay. Now, your Ph.D., as your terminology
9 is -- terminology based in immunology, not molecular
10 biology; right?

11 A. Correct. The program that I was in was an
12 immunology program. It gave me an academic foundation
13 in principles of immunology, both the cellular and
14 molecular. And Epstein-Barr virus is a virus that
15 affects B cells. B cells are part of the adaptive
16 immune system. So my studies were very much related to
17 both immunology and molecular biology.

18 But the laboratory that I did my thesis in
19 would characterize itself as a molecular virology lab.
20 So really, my thesis significantly touched a number of
21 different disciplines, including virology, molecular
22 biology, and immunology.

23 Q. But the name of your Ph.D. is immunology,
24 not molecular biology; right?

25 A. The name of my Ph.D. is immunology. That

1 does not change the fact that the core of my thesis
2 training was really in molecular biology.

3 Q. Okay. You -- I noted that you received a
4 patent in 2007; is that correct?

5 A. That sounds correct.

6 Q. Okay. It says, I think, "Methods to
7 identify regulators of cellular activation using BCL10."

8 Does that sound familiar to you?

9 A. BCL10 --

10 Q. BCL10.

11 A. -- to correct the nomenclature, but, yes,
12 that's correct.

13 Q. Did that patent that you received flow from
14 or have anything do with your Ph.D. research?

15 A. That particular patent did -- was not
16 directly related to my Ph.D. research. I would say that
17 many of the techniques that I learned during my thesis
18 research or -- were used in my subsequent post-doctoral
19 research, and they perhaps assisted me indirectly in
20 that invention.

21 But the invention has nothing do with
22 Epstein-Barr virus. It has nothing to do with promoter
23 identification. It had nothing to do with any of the
24 other direct topics of my Ph.D. thesis.

25 Q. Was -- your co-inventors, were those your

1 post-doc mentors?

2 A. They were my post-doc mentors; correct.

3 Q. Dr. Schaefer, have you ever recombinantly
4 produced proteins in a lab?

5 A. Yes, I've recombinantly produced many
6 proteins in a lab.

7 Q. Have you ever recombinantly produced any
8 horseshoe crab proteins in a lab?

9 A. I have not recombinantly produced horseshoe
10 crab proteins in a lab. But I would again add the fact
11 that the production of proteins recombinantly is mostly
12 species agnostic. And so in order to offer expert
13 opinions about horseshoe crab proteins, I don't
14 necessarily need to have worked on those particular
15 proteins.

16 Q. Excellent.

17 Have you ever created an endotoxin
18 detection assay in a lab?

19 A. I have never created an endotoxin detection
20 assay in a lab. I have used endotoxin detection kits,
21 reagents in a laboratory setting, but I have not been
22 involved with creation of those reagents.

23 Q. And have you ever worked on any projects in
24 which you evaluated endotoxin detection kits relative to
25 other endotoxin detection kits?

1 A. I've been working in a lab for a very long
2 time. But as for as any formal comparison between
3 different endotoxin kits, no, I've never done anything
4 like that.

5 Again, I believe I am familiar enough with
6 the concepts involved in such testing to offer informed
7 opinions.

8 I would also add that I don't think those
9 particular issues are really at the core of what I've
10 offered expert testimony about.

11 Q. Okay. We're going to talk today about the
12 Factor C protein from horseshoe crab -- from the
13 horseshoe crab zymogen protein cascade.

14 Have you ever heard of Factor C before you
15 got involved in this case?

16 A. I -- seeing as I had used the clotting
17 cascade reagents to detect endotoxin, I was loosely
18 familiar with what was in the kit, yes.

19 Q. Okay. The reagents that you used, do you
20 recall if they were the -- based on the native lysate or
21 recombinant protein assays?

22 A. I do not recall. But based on the timing
23 of when I first used those, at least when I first used
24 them, they must have been based on the native enzymes
25 because I don't think the recombinant kits were

1 available yet.

2 Q. Relatively when you're thinking about the
3 time frame, what are you thinking, what time frame?

4 A. Late 1990s. Mid to late 1990s.

5 Q. Okay. We are going to talk about some
6 sequence data that you discuss that was deposited by
7 some researchers from Yukon.

8 Do you know what I'm talking about?

9 A. I know what you're talking about.

10 Q. Okay. Before being involved in this case,
11 did you have any reason or any exposure to that
12 database?

13 A. When you say "that database," can you be
14 more specific?

15 Q. The Yukon deposits of the horseshoe crab
16 sequences that you refer to in this case.

17 A. I had not had any reason to review the
18 Yukon deposits for horseshoe crab sequences.

19 Q. Okay. Do you have any legal training,
20 sir -- Doctor?

21 A. I do not have any legal training.

22 Q. In your declarations, you referred to some
23 legal principles.

24 Do you know what I'm referring to?

25 A. There are some legal principles that are

1 defined in my declaration.

2 Q. And you refer to your understanding of
3 those as being informed by counsel in this matter;
4 right?

5 A. That is correct.

6 Q. Other than the legal principles and the
7 explanation of those by counsel, do you have any other
8 legal background in patent law?

9 A. I have no background in patent law, other
10 than having submitted two, three things for
11 consideration for patents, and a couple of those have
12 become patents. So I have previously worked a bit with
13 patent lawyers on patents, editing the language, you
14 know, giving the initial descriptions. But that was
15 really not in any kind of legal capacity; that was a
16 scientific capacity.

17 Q. Okay. Did you read any legal cases in
18 preparing your declaration in this case?

19 A. No, I did not do that type of review.

20 Q. Okay. Could you turn to paragraph 46 of
21 your IPR declaration.

22 And 46 begins under the section heading C,
23 "Person of Ordinary Skill in the Art."

24 Do you see that?

25 A. I see that.

1 Q. In paragraph 47, you refer to one of the
2 inventors' backgrounds as supporting your view regarding
3 the definition of a person of ordinary skill in the art.

4 Do you see that?

5 A. I do see that.

6 Q. Okay. And the inventor that you refer to
7 is Shun-ichiro Kawabata who has a Ph.D. in biology and
8 experience in biochemistry.

9 Do you see that?

10 A. I see that.

11 Q. Why did you pick that inventor of the three
12 named inventors listed on the '318 patent?

13 A. It's a representative inventor.

14 Q. Okay. Did you look at the educational
15 background of the other two inventors?

16 A. No, I did not look at the background of the
17 other two inventors.

18 Q. Okay. Did you know that the first named
19 inventor, Dr. Mizumura, submitted multiple declarations
20 to the US Patent Office in the prosecution of the '318
21 patent?

22 A. I'm familiar with the fact that
23 Dr. Mizumura submitted many, many such applications,
24 yes.

25 Q. And what was Dr. Mizumura's Ph.D. in?

1 A. I have not reviewed his background
2 extensively.

3 Q. Okay. Are you -- are you aware that he has
4 a Ph.D. in organic chemistry?

5 A. I was not aware of that.

6 Q. Okay. Is it your opinion that a person
7 with a Ph.D. in organic chemistry could also be a person
8 of skill in the art in this case?

9 A. A person with the background --

10 MS. LO: Objection, outside the scope.
11 Sorry.

12 A. I would say that a person with a background
13 in organic chemistry could certainly be a POSA if they
14 have relevant experience working in a field.

15 BY MS. LOUGHRAN:

16 Q. Okay. So it's fair to say, then, that it's
17 not necessarily the name of the Ph.D. that you are
18 granted, but rather your experience that qualifies you
19 as a POSA; correct?

20 A. I don't know that I would phrase it that
21 way. I would say that it is a combination of one's
22 degree and one's experience that qualifies a person as a
23 POSA. The person may have both a degree and experience
24 that qualifies them, or they may have one or the other.

25 I would say that, you know, objective

1 review of person's background can lead you to
2 determining whether or not they are a POSA.

3 Q. Okay. But it's fair to say that just
4 because a person does not have a Ph.D. in the
5 specifically listed Ph.D.s of Seikagaku's proposed
6 definition doesn't preclude them from being a POSA in
7 this field; right?

8 A. I would say that that fact alone does not
9 exclude them from being a POSA. You have to look at the
10 entire background and education of the person
11 collectively.

12 Q. You reference in this case a -- your review
13 of a declaration submitted by a Dr. Frohman?

14 A. Correct.

15 Q. Do you know what his Ph.D. was in?

16 A. I do not recall what Dr. Frohman's Ph.D.
17 was in. I'm very familiar with his published work but
18 I'm familiar with his education.

19 Q. If you were to learn that he had a Ph.D.
20 also in immunology, would you believe that that would
21 preclude him from being a POSA in this case because
22 that's not one of the listed Ph.D.s that patent owner
23 proposes?

24 A. I know Dr. Frohman's scientific background.
25 Again, considering both his education and his scientific

1 training and what he did, he is clearly qualified as a
2 POSA.

3 Q. Now, at paragraph 48, at the end of that
4 paragraph, you say, "Education and experience in
5 biological, chemical, or biochemical engineering, which
6 to my understanding relate to developing industrial
7 scale processes for protein production, is outside of
8 the field and not required."

9 Do you see that?

10 A. I see that.

11 Q. Okay. Now, it may not be required, but
12 experience in those areas could provide requisite
13 experience to be qualified as a POSA under patent
14 owner's definition; right?

15 A. I stand by the statement saying that those
16 things are not required. I did not say anything beyond
17 that.

18 Q. Okay. So just because they're not required
19 doesn't preclude a person who has those experiences from
20 becoming a POSA; right?

21 A. I did not say that, so correct, I agree.

22 Q. You talk in your declaration -- or you
23 refer to having done an article about RACE.

24 Do you remember that?

25 A. I do.

1 Q. I think it was a 1995 publication. Are you
2 familiar?

3 A. That sounds about right.

4 Q. Was that -- the research that went into
5 that publication, did that require any lab work or was
6 that a review article?

7 A. Although it was a review article, it also
8 contains protocol, very detailed methodology for how to
9 optimally conduct RACE PCR at the time.

10 And that methodology section was entirely
11 based on my experience during my Ph.D., many years of
12 experience with RACE, further optimizing the technique,
13 studying what optimizations were out there in the
14 literature, and combining them into what I understood to
15 be the most efficient way to perform RACE, particularly
16 if you were concerned about getting the true 5 prime
17 ends of an mRNA.

18 Q. But that article did not report on any --
19 did not include any results of research -- experimental
20 research that you had done in preparation of that
21 article; correct?

22 A. It was a review article with methodology.
23 The intent was not to present research. If you want
24 research that shows my results with RACE PCR, those were
25 published in several articles during my Ph.D. thesis,

1 including one in PNAS, and I believe a later one in --
2 I'm not sure which article that ended up in, so I'm not
3 going to say. Multiple publications, though.

4 Q. Okay. Now, if you look at paragraph 52 of
5 this declaration, you say, "In my opinion, Claim 21 of
6 the '318 patent is entitled to a December 10, 2013
7 priority date because the disclosure is in the '767
8 application, coupled with what was well understood in
9 the art to a POSA, provides written description,
10 enablement, support for the full scope of Claim 21."

11 Do you see that?

12 A. I see that.

13 Q. You agree that the inventors are persons of
14 skill in the art; right?

15 A. I agree that the inventors are persons of
16 skill in the art.

17 Q. Okay. Now, you also agree that your
18 opinions on written description and enablement, as you
19 refer to them here, do depend on filling in gaps based
20 on knowledge of a person of skill in the art; right?

21 A. Again, I am not sure that I would phrase it
22 exactly that way. The way I would phrase it is that
23 rather than filling in gaps, as you stated, I would say
24 that they would use available resources to, in a very
25 straightforward and rapid manner, assemble the full

1 sequence.

2 Q. But that full sequence had not been
3 published by December 10th, 2013; correct?

4 A. The full nucleotide sequence or full
5 translated sequence had not been published in any
6 peer-reviewed journal. That is an accurate statement.

7 Q. Are you aware of it having been published
8 in any non-peer-reviewed journal?

9 A. I'm not aware of it, but I can't rule it
10 out. I would again say that the information was
11 available, and a POSA would understand that it could be
12 rapidly assembled into a full sequence.

13 Just because something has not been
14 published doesn't mean that it's not available. And, in
15 fact, you know, given that there were two other Factor C
16 sequences from closely related species already
17 published, there is very little incentive for a POSA to
18 try to submit that to a peer-reviewed journal because
19 they would really encounter a lot of headwinds in
20 publishing it because the collective response would be,
21 who cares, we basically already know this.

22 Q. Okay. It didn't appear in any patent
23 publications, either; correct?

24 A. Not to my knowledge.

25 Q. Okay. Just to be clear, your opinions

1 about the level -- we'll get to the sequence in a bit.

2 But your opinions about the definition of a
3 person of skill in the art are the same across both the
4 IPR and the PGR; correct?

5 A. As I recall, we used the same definition of
6 a POSA in both documents.

7 Q. Okay. And does your opinion change in any
8 way depending on whether a patent owner's or a
9 petitioner's definitions are adopted?

10 A. My opinions are not really dependent on the
11 definition of a POSA.

12 Q. Okay. All right. So for the IPR
13 declaration, you -- your opinion in this declaration is
14 that the Claim 21 should be entitled to a December 10th,
15 2013 priority date; right?

16 A. That is my opinion.

17 Q. Okay. Did you form any opinions as to
18 whether Claim 21, if not afforded that earlier priority
19 date, should be afforded any other priority date?

20 A. Any opinions of that sort are in my
21 declaration. If you can point me to specific text that
22 you'd like to ask me about, I'm happy to answer
23 questions.

24 Q. Well, that's sort of my question. I don't
25 see anything in your declaration that says that you

1 think that Claim 21 should be afforded any other
2 priority dates. So I just wanted to verify with you
3 that your opinions are only about December 2013.

4 A. My opinions are focused on the
5 December 2013 priority date. The opinions of
6 Dr. Tina Morris were focused on the possibility of a
7 later priority date.

8 Q. Okay. Now, you do provide some opinions on
9 obviousness if the December 13th -- December 2013
10 priority date is -- is deemed to be incorrect; right?

11 A. Again, you can point me to specific
12 sections in my declaration.

13 Q. Yep. You can look at, for example -- I
14 think these start on page 58, paragraph 119.

15 Do you see where paragraph 119 is?

16 A. I do see that.

17 Q. Okay. This section basically says,
18 "Claim 21 is not obvious over Mizumura in view of the
19 498 PCT."

20 Do you see that?

21 A. I do see that.

22 Q. And then later at paragraph -- on page 61,
23 you have a section that says, "Claim 21 is not obvious
24 over Mizumura in view of McClymont."

25 Do you see that?

1 A. Yes.

2 Q. Now, these opinions are based on
3 deficiencies -- my understanding is these opinions are
4 based on deficiencies that you found in Dr. Jain's
5 opinions; correct?

6 A. I disagree with the number of Dr. Jain's
7 opinions.

8 Q. Okay. But do you have any separate
9 opinions about whether or not those prior art references
10 actually teach the limitations of Claim 21?

11 A. Can you point me to exactly what you're
12 discussing here?

13 Q. Well, again, I'm just asking you to confirm
14 that you didn't form any opinions about that fact.

15 A. My arguments are mostly focused on the
16 priority date. I do have some arguments related to
17 obviousness.

18 Q. Okay. Did you form any opinions about
19 whether a POSA would have had a reason to combine these
20 prior art references?

21 A. Can you point me to the part of my
22 declaration where I discuss that?

23 Q. Well, I can't. I'm just asking whether you
24 formed any opinions on that fact.

25 A. I haven't really thought about that.

1 Q. Okay. Dr. Schaefer, are you aware that
2 patent owner is pursuing an alternate Claim 22 if
3 Claim 21 is found unpatentable?

4 A. I've been made aware of that. My
5 understanding is that the Claim 22, the substitute
6 claim, is very, very similar to the Claim 21, but that
7 the language has been slightly adjusted.

8 I have not studied that claim in detail, so
9 I can't offer any opinions on it, but I'm aware it
10 exists.

11 Q. Have you reviewed the language of Claim --
12 proposed Claim 22?

13 A. Not carefully.

14 Q. But you've seen it?

15 A. I believe I had it read to me.

16 Q. Read to you?

17 A. Yes.

18 Q. Okay. And you said you've been made aware
19 about Claim 22.

20 Were you aware of it when you signed this
21 declaration?

22 A. I don't believe I was.

23 Q. So you were made aware of it after
24 submitting this declaration?

25 A. Yes.

1 Q. So it would be fair to say that nothing in
2 this declaration includes your opinions about the
3 patentability of Claim 22; right?

4 MS. LO: Objection to form.

5 A. I don't really know how to answer that
6 question because what I understand of Claim 22 is that
7 it's extremely similar to Claim 21. So without
8 extensive review of the exact language, I don't really
9 know how to answer that.

10 BY MS. LOUGHRAN:

11 Q. Well, let me ask it a different way.

12 You didn't know about Claim 22 when you
13 signed this declaration, right, as you just testified?

14 A. I would say I did not know about Claim 22
15 when I wrote the declaration. But at the same time, the
16 language of substitute Claim 22 sounded so similar to me
17 that I'm hard-pressed to say that my scientific
18 conclusions would be any different. To me, it sounded
19 like the claim may have changed legal meanings but not
20 the scientific thrust.

21 But, again, without having Claim 22 in
22 front of me and studying it, I don't really know how to
23 answer your question.

24 Q. When you signed this declaration -- well,
25 strike that.

1 You acknowledge that Claim 22 is different
2 than Claim 21; right?

3 A. There are different words in Claim 22 than
4 Claim 21. They are not identical. I do acknowledge
5 that.

6 Q. And you did not have any awareness of what
7 Claim 22 said when you signed this declaration; right?

8 A. To my recollection, that is correct.

9 Q. So you could not have formed opinions about
10 Claim 22 when you signed your declaration; correct?

11 A. I don't know that I would say it that way
12 because if the thrust of Claim 22 is the same as
13 Claim 21, then my opinions on Claim 21 can be
14 transferred, part and parcel, to Claim 22.

15 Again, without studying the precise
16 language, I don't think I can really answer your
17 question.

18 Q. Sitting here today, can you tell me which
19 of your opinions in this declaration would apply to
20 Claim 22?

21 A. That sounds like a different version of the
22 same question that you just asked, so I would say that I
23 have answered that question.

24 If we go with the assumption that the
25 thrust of Claim 22 is the same as the thrust of

1 Claim 21, then I would say that absolutely everything I
2 wrote about Claim 21 would apply to Claim 22.

3 But, again, I have not reviewed Claim 22,
4 and I have not had discussion with the legal team here
5 about what is really different about Claim 22 than
6 Claim 21.

7 Q. So you can't tell me today which of your
8 opinions in this declaration would apply to Claim 22;
9 right?

10 A. I cannot tell you definitively which of my
11 statements would apply to Claim 22. But, again, if the
12 thrust of Claim 22 is identical to the thrust of
13 Claim 21, then I would say that they all do.

14 Q. Do you have an opinion on whether Claim 22
15 is broader or narrower than Claim 21?

16 A. I have no --

17 MS. LO: Objection, outside --

18 A. -- opinion on this matter.

19 BY MS. LOUGHRAN:

20 Q. But you did study Claim 21 of the '318
21 patent; right?

22 A. I did study Claim 21, yes.

23 Q. Okay.

24 (Exhibit 1001 was given to the witness.)

25 BY MS. LOUGHRAN:

1 Q. I'm going to hand you a document that's
2 been premarked Exhibit 1001. It's the '318 patent in
3 the IPR.

4 Do you recognize this document?

5 A. Yes. It does appear to be the complete
6 text of the '318 patent.

7 Q. Great.

8 Now, if you turn to the very end,
9 second-to-last page, you'll see Claim 21 there.

10 Do you see that?

11 A. Yes.

12 Q. Okay. And you agree that this claim
13 requires a Factor C protein that has, quote, "activity
14 of Factor C"; right?

15 A. Yeah, this claim would appear to require a
16 Factor C protein that has an activity of Factor C.

17 Q. And per the '318 patent, activity of
18 Factor C requires detecting endotoxin; right?

19 MS. LO: Objection to form.

20 A. That terminology could be interpreted a
21 number of ways. I would ask you to rephrase your
22 question in a more precise manner.

23 BY MS. LOUGHRAN:

24 Q. Okay. Well, when Claim 21 uses the phrase
25 "activity of Factor C," that means the detection of

1 endotoxin; right?

2 MS. LO: Objection to form.

3 A. As a scientist, I would use more precise
4 language. For Factor C to have the activity of
5 Factor C, it must bind to LPS. That binding of LPS will
6 cause its activation. And the activation being its
7 activation as protease, so it can then be measured by
8 cleaving an appropriate substrate such as a chromogenic
9 substrate.

10 BY MS. LOUGHRAN:

11 Q. All right. Now, the '318 patent and -- LPS
12 is -- we'll use the phrase LPS, which is a component of
13 endotoxin; correct?

14 A. Yes.

15 Q. Okay. Does Claim 21 put any limitation on
16 the type of endotoxin that -- from which LPS -- well,
17 let me strike that.

18 Does Claim 21 put any limitation on the
19 type of LPS or from what type of endotoxin it must come
20 from in order for Factor C to have activity of Factor C?

21 MS. LO: Objection, outside the scope.

22 A. I do not see in the claim any type of
23 description of the stimulating material. All it says is
24 that the Factor C has the activity of Factor C.

25 BY MS. LOUGHRAN:

1 Q. Yeah. So not a trick question.

2 So LPS could be from like naturally
3 occurring endotoxin; right?

4 A. I believe that would be the main LPS we
5 would be concerned with is naturally occurring endotoxin
6 that contaminates any of a variety of medical devices or
7 things that are put into patients. Yes, naturally
8 occurring LPS would be included.

9 Q. Okay. It could also -- LPS could also be
10 from standardized endotoxin; right?

11 A. Certainly. When you're performing these
12 assays, you use an endotoxin standard so that you have a
13 control and a point of reference.

14 Q. Okay. Did you do any experiments -- we'll
15 talk about some of the sequence data and analysis that
16 you did.

17 But did you do any sort of wet lab
18 experiments in the course of forming your opinions that
19 appear in your declarations in this case?

20 A. That's a very vague and open-ended
21 question. Can you make your question more specific?

22 Q. Sure.

23 Did you perform any research experiments
24 with any zymogen proteins in forming the opinions that
25 appear in your declaration?

1 A. I would ask you to clarify again. Are you
2 specifically talking about zymogen proteins that are
3 horseshoe crab proteins or related to horseshoe crab
4 proteins?

5 Q. I just want to know if you did any
6 experiments that inform your opinions that are not
7 discussed in your declaration.

8 A. I see. No, I did not do any wet lab
9 experiments during the course of preparing this
10 declaration that would inform -- specifically inform my
11 opinions that are given in the declaration.

12 Q. Did you do any such wet lab experiments
13 between signing your declaration and testifying today?

14 A. No, I did not do any type of experiment of
15 that sort.

16 Q. Okay. I'm going to hand you another
17 exhibit, which is a large one, but it is the -- been
18 premarked Charles River Exhibit 1006 in the IPR. It is
19 the '767 application as filed.

20 A. Yes.

21 (Exhibit 1006 was given to the witness.)

22 BY MS. LOUGHRAN:

23 Q. Do you recognize this document, Doctor?

24 A. I do.

25 Q. Okay. So this is the '767 application that

1 you refer to in your declarations; right?

2 A. It does appear to be.

3 Q. Okay. And this is the application that was
4 filed that gave rise to the '318 and '109 patents;
5 right?

6 A. That is my understanding.

7 Q. Okay. And your opinions are that this
8 application, when it was filed, provide adequate written
9 description and enablement support for Claim 21; right?

10 A. That is correct.

11 Q. And, also, you have the opinion that this
12 application, when it was filed, provides adequate
13 written description, enablement, support for Claims 1
14 through 9, the challenged claims of the '109 patent;
15 correct?

16 A. That is correct.

17 Q. And the '767 application that you have in
18 front of you is substantively identical to the
19 specification of the '318 and '109 patents; right?

20 A. That is correct.

21 Q. Now, you understand that the application as
22 filed that you have in front of you was the inventors'
23 chance to tell the world what they had invented; right?

24 A. I suppose you could state it that way.

25 Q. Okay. And you agree that the '767

1 application doesn't explicitly provide any sequence
2 information about Limulus polyphemus horseshoe crabs;
3 right?

4 A. The '767 application does not include a
5 specific Factor C sequence from Limulus polyphemus. It
6 does include an explicit sequence from Tachypleus. And
7 a POSA would understand that the inventors possessed the
8 full scope of the invention because the sequence from
9 Limulus could easily be obtained from databases with
10 boilerplate methodology.

11 Q. Okay. The inventors themselves didn't put
12 the Limulus polyphemus sequence into their application;
13 right?

14 MS. LO: Objection, asked and answered.

15 A. As I stated, the inventors did not
16 specifically put that sequence in their patent
17 application.

18 As I understand patent law, they did not
19 need to put it in their patent application because a
20 POSA would have understood that they could easily obtain
21 this information. And once obtaining this information,
22 they could perform the invention that was described by
23 the inventors.

24 BY MS. LOUGHRAN:

25 Q. Now, the inventors also didn't explicitly

1 describe making any recombinant zymogen proteins from
2 Limulus polyphemus in their application; right?

3 A. The inventors described methodology in
4 their application for producing horseshoe crab proteins
5 rather generically, giving the example of producing
6 proteins from Tachypleus.

7 And, again, a POSA would understand that
8 that methodology could be applied to the proteins from
9 any other horseshoe crab, given that the inventors
10 stated that that is what someone should do to carry out
11 this invention and given that the information to obtain
12 the sequences from other crab species was either already
13 published or could easily be assembled.

14 Q. I understand that you're going to continue
15 to give this answer, but I just want to ask you very
16 specifically that the inventors did not put into this
17 application anything describing their recombinant
18 production of Limulus polyphemus zymogen proteins; is
19 that fair?

20 MS. LO: Objection, asked and answered.

21 A. I will continue giving the same answer,
22 which is that it is true that information of that sort
23 pertaining specifically to Limulus was not present in
24 the application, but a POSA would have understood that
25 it was easily obtainable. And it's not required that

1 that information be present in the application.

2 BY MS. LOUGHRAN:

3 Q. Sitting here today, you could not point to
4 anything in the application in front of you, the '767
5 application in front of you, that is sequence
6 information for Limulus polyphemus; right?

7 A. Give me a moment to look through the
8 application.

9 What I do not recall and what I'm not
10 specifically finding is whether the tryptic peptide
11 sequence from Tokunaga was specifically included in
12 these materials or whether that publication was simply
13 referenced.

14 But certainly within the application, there
15 is information that connects a POSA to the Tokunaga
16 publication where tryptic peptide sequences from the
17 N-terminus are found. So there is some sequence
18 information from Limulus that is connectible to this
19 application.

20 Q. But as far as actual sequence listings for
21 Limulus polyphemus, they do not appear in this
22 application; right?

23 A. If you're asking whether there is an entire
24 sequence for any Limulus protein in this application,
25 no, there is not. There are representative examples

1 from Tachypleus.

2 And, again, a POSA could use published
3 information to find the complete sequences or a
4 combination of public -- published information plus
5 boilerplate techniques like lambda phage library
6 screening or RACE PCR combined with PCR with -- standard
7 PCR with primers from the sequences gathered from RACE
8 PCR to generate the full sequences from each of the
9 Limulus proteins that is referenced in this application.

10 Q. You agree that the information provide in
11 this application about the Tachypleus horseshoe crab is
12 outside the scope of the Claim 21; right?

13 A. In Claim 21, Tachypleus is not specifically
14 mentioned. Limulus is the specific species of crab that
15 is mentioned.

16 Q. Do you have an awareness of what we mean
17 when we talk about claim scope?

18 A. I have some awareness; but if you would
19 like to give me your concise definition, that would be
20 helpful.

21 Q. So if I made the proteins that were
22 described in this application, the Tachypleus proteins
23 that were described in this application, those would not
24 infringe Claim 21; right?

25 MS. LO: Objection, outside the scope. No

1 infringement at issue here.

2 A. I choose not to offer an opinion on that
3 because it's not related to my declaration.

4 BY MS. LOUGHRAN:

5 Q. Well, you do have to answer the question,
6 though. You can't choose not to answer a question.

7 A. You're asking me a legal question that is
8 not really related to my declaration. You're going to
9 have to rephrase this in a way that does not use the
10 word "infringement."

11 What do you really mean in scientific
12 terms?

13 Q. Claim 21 requires a horseshoe crab Factor C
14 protein having activity at Factor C wherein the
15 horseshoe crab is *Limulus polyphemus*.

16 You understand that; right?

17 A. I understand that.

18 Q. That would not include a recombinant
19 Factor C protein wherein the horseshoe crab is
20 *Tachypleus tridentatus*.

21 Do you understand that?

22 MS. LO: Objection to form.

23 A. Claim -- Claim 21 does not mention
24 *Tachypleus*.

25 BY MS. LOUGHRAN:

1 Q. Now, there's nothing in the '767
2 application that describes the inventors having measured
3 the residual activity of any *Limulus polyphemus*
4 recombinantly produced protein; right?

5 A. The inventors wrote their patent in such a
6 way that a POSA would understand that all of their
7 findings, all of their directions, every aspect of their
8 invention applied equally, not only to the specific
9 examples that they showed of *Tachypleus*, but also to the
10 other crab species that they called out and named
11 specifically and included in their invention,
12 specifically *Limulus*.

13 Q. Can you point me to any residual activity
14 data in this application for *Limulus polyphemus*
15 recombinantly produced proteins?

16 A. The data that the authors of the patents
17 have included include residual activity data for
18 *Tachypleus*. And, again, they included those as
19 examples. And a POSA would understand those examples to
20 be applicable to other crab species.

21 Q. Sir, I do need you to answer my question.
22 Can you point to me any residual activity
23 data in this application for *Limulus polyphemus*
24 recombinant proteins?

25 It's just a yes-or-no question.

1 MS. LO: Objection, asked and answered. I
2 think he did answer the question.

3 A. I will give the same answer: Although
4 there are no data that specifically show residual
5 activity for Limulus, a POSA would understand that the
6 data that are shown for Tachypleus would be applicable
7 to other crab species, including Limulus, other
8 horseshoe crab species.

9 BY MS. LOUGHRAN:

10 Q. By the way, did you have an awareness of
11 what the term "residual activity" meant before you read
12 the '318 patent?

13 A. The term "residual activity" was not one
14 that was familiar to me. Conceptually, it's quite
15 simple. And, you know, it's basically just measurement
16 of activity in comparison to a control.

17 So I did not have any difficulty
18 understanding it, but that was the first time I had
19 heard those kind of data expressed with those particular
20 words.

21 Q. And those particular words being --

22 A. Residual activity.

23 Q. -- "residual activity"?

24 A. Yes.

25 MS. LO: We've been going a little over an

1 hour.

2 MS. LOUGHRAN: I was just contemplating
3 that. Let's take a short break.

4 We'll go off the record and come back at
5 11:20 -- or I guess 10:20.

6 (A break was taken.)

7 BY MS. LOUGHRAN:

8 Q. Hello again, Dr. Schaefer. How are you?

9 A. I'm good. How are you?

10 Q. Good.

11 Did you discuss the substance of your
12 testimony over the break with Ms. Lo?

13 A. We did not.

14 Q. I believe we were talking about the '767
15 application. And you do agree that this application
16 contains the sequence -- amino acid and cDNA sequence
17 information for Tachypleus; right?

18 A. The application does contain Tachypleus,
19 cDNA, and protein sequences, yes, I agree.

20 Q. And it does also contain sequence
21 information for Carinoscorpius; correct?

22 A. It also contains some sequence information
23 for that other Asian species, yes, that is correct.

24 Q. And I know you understand that it doesn't
25 contain the sequence information for Limulus polyphemus,

1 but you believe a POSA would have been able to arrive at
2 that information; right?

3 A. I agree with the statement you made, yes.

4 Q. Okay. One explanation for why this
5 application does not include Limulus polyphemus sequence
6 information is because the inventors didn't have it; is
7 that fair?

8 MS. LO: Objection to form.

9 A. I would not make that statement. I would
10 not speculate about why it is not in this application.
11 All I would say is that a POSA would know that it was
12 readily and easily available through a combination of
13 sequence deposits and use of PCR methodology or
14 alternative methods such as lambda phage screening.

15 BY MS. LOUGHRAN:

16 Q. But wouldn't you expect if the inventors
17 had that sequence information, they would put it in
18 their application?

19 MS. LO: Objection, calls for speculation.

20 A. I don't know what the inventors were
21 thinking. I don't know the inventors' reasons for doing
22 anything that they did, so I don't know how to answer
23 that question.

24 BY MS. LOUGHRAN:

25 Q. Okay. Earlier this morning, you used the

1 words -- you said -- we were talking about Claim 21 and
2 proposed new Claim 22, and you discussed the thrust of
3 the claim.

4 Do you recall that?

5 A. I did use the word the "thrust," yes.

6 Q. Okay. What is your understanding of the
7 thrust of Claim 21?

8 A. Well, we can read Claim 21 together again.
9 I believe Claim 21 is pretty clear in its language.

10 So reciting Claim 21, "A horseshoe crab
11 Factor C protein having activity of Factor C wherein the
12 horseshoe crab is *Limulus polyphemus*, and wherein the
13 horseshoe crab Factor C protein is produced through
14 being recombinantly expressed from Human Embryonic
15 Kidney cell (HEK) 293, and wherein the Factor C protein
16 exhibits a residual activity of at least one selected
17 from the group consisting of 10 percent or higher in the
18 presence of 21 millimolar sodium citrate and 15 percent
19 or higher in the presence of 16 millimolar magnesium
20 sulphate."

21 So that word-for-word is what Claim 21
22 says.

23 Q. Right.

24 And so it's your position that when you
25 were testifying about the thrust of Claim 21, it is the

1 word-for-word recitation of that claim?

2 A. Thrust does not mean word for word. Thrust
3 means what a POSA, for example, would understand from
4 the language, what is meant by the language.

5 Q. Okay.

6 A. That's what I mean by "thrust."

7 Q. Okay. So what would a POSA understand from
8 the language in this claim as to what is meant by this
9 language?

10 MS. LO: Objection, form.

11 A. I believe I have read the claim word for
12 word. What I would say is you could make some minor
13 adjustments to the language, perhaps for legal purposes.

14 But we would still be talking about a
15 horseshoe crab protein that has the activity of a
16 Factor C. We would still be talking about that the
17 horseshoe crab is *Limulus polyphemus*. We would still be
18 talking about expressed from Human -- HEK293 cells. And
19 we would be talking about the specific residual
20 activities that are called out by the inventors.

21 To my recollection, none of those items
22 that I have just recited are different in the alternate
23 Claim 22, but I would have to inspect Claim 22 to say
24 that with absolute certainty.

25 BY MS. LOUGHRAN:

1 Q. Could you turn to paragraph 56 of your
2 declaration in the IPR, please, Doctor?

3 A. Fifty-six, you said?

4 Q. Yes, please.

5 You say, "The '767 application further
6 includes an example of expression of Factor C in
7 mammalian cells. This section describes steps to
8 produce Factor C using HEK 293 cells as the host cell,
9 which is the same host cell recited in Claim 21."

10 Do you see that?

11 A. Yes.

12 Q. The example here is an example of
13 expression of Tachypleus Factor C; right?

14 A. That is the example that is provided, yes.

15 Q. And in paragraph 57, you talk about, "The
16 application includes an example titled Inhibition of
17 Activity by Injection that details measuring the
18 residual activity of Factor C in the salt solutions,
19 including the claim's 21 millimolar sodium citrate and
20 16 millimolar magnesium sulfate."

21 Do you see that?

22 A. I see that.

23 Q. And, again, that example is with a Factor C
24 recombinantly produced from the Tachypleus crab; right?

25 A. That is what the example shows, correct.

1 Q. Okay. Now, if you could look at the data
2 that is provided in the application from those
3 measurements. And you reproduce it at the next page of
4 your declaration, so you could just look at that.

5 Do you see that?

6 A. I see that.

7 Q. And you've reviewed this figure in
8 preparing your testimony today; right?

9 A. I have.

10 Q. And you reviewed this figure in preparing
11 your declaration in which it appears; right?

12 A. Correct.

13 Q. Okay. Would you agree that Factor C
14 recombinantly produced in mammalian cells has higher
15 residual activity than in native lysate?

16 A. Are we talking about the specifically boxed
17 sections, number 2 and number 5?

18 Q. Well, we can start with number 2 and 5.

19 In 2 and 5, does this show that
20 recombinantly produced Factor C has a higher residual
21 activity than in native cells -- or native Factor C?

22 A. Two specific mammalian cell lines are
23 called out. That is CHO-DG44 and HEK293.

24 So as pertains to those specific cell
25 lines, that is what is specifically shown in this

1 figure.

2 Q. Okay. And, in fact -- now, you read the
3 applicant's -- the application that gave rise to this
4 patent; correct?

5 A. I did.

6 Q. And the inventors described their
7 invention, right, in that application?

8 A. They did.

9 Q. Fair to say that the inventors were
10 describing the better residual activity that you -- that
11 they saw when producing Factor C via mammalian cells and
12 compared to native lysate.

13 Is that a fair description of what they
14 thought was invented?

15 MS. LO: Objection to form.

16 A. A number of times, the inventors call out
17 the superior activity of Factor C expressed in mammalian
18 cell lines versus insect cells and versus the native
19 lysate, and they specifically refer to these data that
20 we're discussing now.

21 BY MS. LOUGHRAN:

22 Q. Okay. And just to be clear, when we talk
23 about this data and residual activity, is it your
24 understanding that residual activity is a measure of ion
25 resistance?

1 A. I don't know that I would use that exact
2 phrasing to describe residual activity because the words
3 you used are brief and somewhat vague.

4 But more specifically, residual activity is
5 the measure of activity, in this specific case of
6 Factor C, of Factor C in a solution that contains
7 particular inhibitors, in some cases ions, relative to
8 the activity of Factor C in pure water.

9 Q. Okay. And the inventors showed that when
10 they recombinantly produced Tachypleus Factor C in
11 mammalian cells, the residual activity was higher
12 relative to residual activity in native Tachypleus
13 lysate; right?

14 A. What you describe is accurate for the
15 specific cell lines that they show, CHO-DG44 and HEK293.
16 Both of those are mammalian cell lines, and they had
17 higher residual activity than the Factor C produced in
18 either the insect line, Sf9, or a purified Factor C from
19 crab blood.

20 Q. Okay. And that comparison is same species;
21 right?

22 So the sequence information for the
23 mammalian expressed Factor C is the same as the sequence
24 information from the native or the Sf9 expressed; right?

25 A. The protein sequences used, to my

1 understanding, were the same across cell lines for the
2 recombinant form.

3 Q. Okay. So holding sequence constant,
4 meaning same sequence, the inventors showed that you
5 could get different residual activity depending on
6 whether you were expressing recombinantly in mammalian
7 cells or you were using native lysate or Sf9 insect cell
8 expression; correct?

9 A. What you describe is one of the main
10 features that they call out in their invention. The
11 superior residual activity that was detected in
12 mammalian cells lines CHO-GD44 and HEK293 versus the
13 insect line Sf9.

14 Q. Okay. Now, Claim 21 provides two options
15 for residual activity of the claimed protein. And I
16 believe you read this, but it's either the protein that
17 has a residual activity of 10 percent or higher in the
18 presence of 21 millimolar sodium citrate or 15 percent
19 or higher in the presence of 16 millimolar magnesium
20 sulfate; right?

21 A. The way you read Claim 21 does not agree
22 with the text of Claim 21.

23 The text of Claim 21 says, "Exhibiting a
24 residual activity of at least one selected from the
25 group consisting of 10 percent or higher in the presence

1 of 21 millimolar sodium citrate and 15 percent or higher
2 in the presence of 16 millimolar magnesium sulfate."

3 I prefer to stick with the exact wording of
4 the claim.

5 Q. Does Figure 7 show that for the Tachypleus
6 recombinantly produced Factor C in HEK293, that that
7 protein satisfies the residual activity thresholds
8 called out in Claim 21?

9 A. So for sodium citrate, which is number 5,
10 the residual activity for HEK293 appears to be around
11 25 percent, and that's greater than 10 percent.

12 And for magnesium sulfate, the threshold
13 that they call out is 15 percent, and what I see there
14 for HEK293 appears to be 20 to 25 percent, particularly
15 if you include the error bar.

16 Q. So the data that they put in Figure 7
17 satisfies the claim, right, for Tachypleus?

18 A. That is my interpretation, that it
19 satisfies the claim, yes.

20 Q. Now, just if we look at, for example,
21 lane 5 here in Figure 5, if you had or -- if the
22 inventors had shown HEK293 residual activity of, let's
23 say, 9 percent -- do you see that?

24 A. I see 5. You're asking me to speculate,
25 yes.

1 Q. In your head, imagine that it says
2 9 percent; okay?

3 A. Okay.

4 Q. That would be greater than the residual
5 activity for Sf9 and native, correct, what's shown
6 there?

7 A. Based on the -- my guesstimation of the
8 height of those bars, yes, I would agree with that.

9 Q. Nine percent would be higher than Sf9 and
10 TAL; right?

11 A. Yes.

12 Q. But that Factor C would not satisfy
13 requirement 1 of Claim 21; right?

14 A. It would not appear to.

15 Q. Okay. And, likewise, I think that you said
16 that for lane 2, HEK -- the residual activity in HEK for
17 magnesium sulfate was about 20 to 25; is that fair?

18 A. If you include the error bar, yes, I
19 believe that's what I said.

20 Q. Okay. And so if you had a Factor C
21 recombinantly produced in HEK cells that had a residual
22 activity of, say, 19 percent, or, let's say, 14 percent,
23 that would be greater than Sf9 and TAL shown in row 2 --
24 in lane 2; correct?

25 A. I guess if we call it the TAL, about 11 or

1 12 percent, yes, that would still be true.

2 Q. Okay. And that would not satisfy the claim
3 requirement for 15 percent or higher in the presence of
4 16 millimolar magnesium sulfate for Claim 21; correct?

5 A. Correct, it would not satisfy the
6 requirement as written.

7 Q. Okay.

8 A. What's written is the threshold value and
9 it's below the threshold value. You have to be above
10 the threshold value.

11 Q. Sir -- or, Doctor, did you -- when you
12 reviewed the '767 application, did the inventors provide
13 any results or data in which they showed the residual
14 activity of recombinantly produced Factor C in a
15 solution that included both magnesium sulfate and sodium
16 citrate?

17 A. That combination does not appear to be in
18 this figure, and I do not specifically recall whether
19 that combination was elsewhere in the application. I
20 also don't think that that specific combination is
21 called out. It's called out in Claim 21.

22 Q. Okay. But so just sitting here today,
23 you're not aware of any data or information in the '767
24 application that shows what the residual activity would
25 be for a recombinantly produced Factor C protein in HEK

1 that is in a solution that includes both of those ions
2 at those concentrations?

3 A. I don't recall whether or not those data
4 are there, but I don't specifically remember that.

5 Q. Okay. Dr. Schaefer, you are not a marine
6 biologist; right?

7 A. I have a number of qualifications; marine
8 biology is not among those. I would add that I don't
9 think extensive knowledge of marine biology is necessary
10 for any of the opinions that I've offered.

11 Q. Okay. Have you ever worked with horseshoe
12 crabs directly?

13 A. I have never worked with horseshoe crabs
14 directly. I've worked with a lot of different animals,
15 but horseshoe crabs are not among them. Again, I don't
16 think that having worked with horseshoe crabs is
17 necessary to offer expert opinions in this matter.

18 Q. You talk in your declaration about
19 horseshoe crabs being considered living fossils; right?

20 A. That is correct.

21 Q. So you do talk a bit about the evolutionary
22 history of the horseshoe crab; right?

23 A. I talk a bit about that, yes, that's
24 correct.

25 Q. And, in fact, you cite an article by Obst,

1 et al., that talks about some of the evolutionary
2 history of horseshoe crabs.

3 I will hand you a document that's been
4 marked Exhibit 2044 in the IPR. It's also -- it's also
5 an exhibit in the PGR.

6 A. Thank you.

7 (Exhibit 2044 was given to the witness.)

8 BY MS. LOUGHRAN:

9 Q. Do you recognize this document, Doctor?

10 A. I do.

11 Q. Okay. And so, for example, at paragraph 20
12 in your declaration, also at paragraph 64 and 85, you
13 talk about the low divergence rates of horseshoe
14 crabs --

15 A. Yes.

16 Q. -- is that accurate?

17 A. That is accurate.

18 Horseshoe crabs have a long generation
19 time, which is cited as the reason for that slow rate of
20 divergence.

21 Q. Okay. And the slow rate of divergence you
22 use to inform some of your opinions about why some of
23 the sequence information is similar as between species
24 of crabs; right?

25 A. I cite that information more as background

1 information that a POSA would know to understand that
2 comparing horseshoe crabs among the great variety of
3 animals out there, you would expect horseshoe crabs to
4 evolve more slowly -- you know, in the grand scheme of
5 things, more slowly than other animals.

6 And so for that reason, even for crab
7 species that have been separated by a certain amount of
8 evolutionary time, the amount of sequence divergence
9 would be lower than you might otherwise anticipate.

10 Q. And this article discusses a divergence
11 rate of about .21 percent per million years; right?

12 A. I don't recall the exact numbers, but I do
13 see that in the discussion, yes.

14 Q. Okay. And I think if you look at some of
15 the figures in this document, for example, at page 5 of
16 6, they show *Limulus polyphemus* diverging from the other
17 species of crab; right?

18 A. That's an accurate assessment of what is
19 shown. I mean, if we're going to be more accurate,
20 there's some divergence between all of the species. But
21 *Limulus* is shown as being somewhat more divergent, which
22 is not surprising, given that it was geographically
23 separated from the other three species that are Asian.

24 Q. Okay. Is it fair to say that *Limulus*
25 diverged approximately, let's see, about 130 to

1 150 million years prior to the divergence of the other
2 species?

3 A. Well, if you're pointing to somewhere in
4 the text -- I see that.

5 Q. Yep.

6 A. That is what the text says, and I don't
7 have any reason to dispute that.

8 Q. Okay. So at .21 percent per million years
9 over roughly, we'll say, slight -- more than a hundred
10 million years, you would get something along the lines
11 of a 21 percent divergence; right?

12 A. If you're talking about the genome as a
13 whole, I don't think I disagree with your math. But,
14 you know, remember, we're talking about the genome as a
15 whole. That is not simply coding sequences. Most of
16 our genomes, us and crabs included, are noncoding
17 sequences. And most divergence is focused in those
18 noncoding sequences.

19 If you take it even a step further, we have
20 to think about what are the functions of the different
21 proteins in the crab. So, for example, things that
22 control shape and color may or may not be selected for
23 or selected against because they may not be that
24 important for survival or they may.

25 In the case of clotting cascade, we know

1 that the clotting cascade is absolutely crucial for the
2 survival of the crabs. So when you have enzymes like
3 that that are crucial to survival, there is evolutionary
4 selection against mutation, and that's a concept known
5 as purifying selection.

6 And you can add on top of that, in addition
7 to just the necessity of this cascade for survival, you
8 have a cascade of proteins which have to sequentially
9 interact with each other. So the ability of those
10 proteins to interact with each other is also conserved
11 over time.

12 So there's actually many, many factors that
13 are acting on these particular proteins to preserve
14 their sequence over time, particularly the key
15 functional domains.

16 Q. And with respect to those key functional
17 domains, you acknowledge that there will be some
18 divergence; right?

19 There is not an identity between those
20 domains as it crosses species; correct?

21 A. Certainly. Over time, there will be some
22 divergence. That divergence is going to tend to be
23 focused on amino acids that, for example, if they're
24 mutated and they don't change the overall structure of
25 the molecule, that's going to be tolerated. Or if they

1 have some other impact that does not change the function
2 of the molecule, they're going to be tolerated.

3 So there's not a clean yes/no answer to
4 that question. It's a "yes-but." The changes that are
5 going to be tolerated are ones that are not going to
6 affect function.

7 Q. Okay. But even in the scenario where there
8 is a change -- or let me strike that.

9 You agree, though, that for those
10 functional proteins, a change in an amino acid, a
11 mutation, a difference in amino acid between species can
12 lead to functional differences; right?

13 A. If we're talking about -- if we're simply
14 talking about genetics, irrespective of what protein
15 we're talking about, for any given protein, if you
16 mutate an amino acid and that amino acid is in a
17 functional domain, it is possible that it will change
18 the function of the protein.

19 Again, I will come back to the idea that if
20 we're talking about a protein that is critical for
21 survival of the species, and if we're talking about a
22 protein that's in a cascade where it has to interact
23 with other proteins that are in that cascade, that
24 cascade, which is required for survival, is highly
25 unlikely that you're going to get a meaningful

1 functional change.

2 Q. But you acknowledge that it is possible;
3 right?

4 MS. LO: Objection, asked and answered.

5 A. I will answer, again, perhaps a little more
6 concisely, saying that if we're talking in general about
7 a protein, you change the sequence of that protein, you
8 can change the function; but for a protein where the
9 function is important for survival, that outcome is very
10 unlikely.

11 BY MS. LOUGHRAN:

12 Q. And you, in fact, have done research in
13 which you have shown single amino acid differences in
14 proteins have led to differences in function; right?

15 A. Certainly. I published several papers that
16 include such data, yes.

17 Q. Okay. I'd just like to mark one. We're
18 going to mark this as Exhibit 1066.

19 (Exhibit 1006 was shown to the witness.)

20 A. And I would point out that the goal of this
21 study, other such studies, is to identify key functional
22 domains. I probably would not have picked this
23 particular publication. I would have picked an older
24 one where we were attempting to identify functional
25 domains of the protein BCL10.

1 And in that case, we intentionally mutated
2 various amino acids to try to elucidate which of those
3 were important for function and get some insights,
4 perhaps, into why: Were these important sites for
5 protein-protein interactions; were they important for
6 structural integrity, those kinds of questions.

7 BY MS. LOUGHRAN:

8 Q. Okay. But just with respect to the article
9 that I put in front of you as Exhibit 1066, you -- if
10 you look at the discussion in this article, you
11 summarize the results of your research and that -- and
12 you say, "The amino acid substitution impacts the
13 spectrum of antibodies capable of interacting with this
14 site." I think you're talking about particular rabies
15 viruses in this article.

16 So you do agree that single amino acid
17 substitutions can have an impact on protein function;
18 right?

19 MS. LO: Dr. Schaefer, if you need to take
20 the time to review this article, please do so.

21 A. So the types of mutations that you're
22 referring to there and their recognition by antibodies,
23 in this case, we're talking about antibodies that are
24 elicited in individuals in response to a rabies vaccine.

25 BY MS. LOUGHRAN:

1 Q. Uh-huh.

2 A. So in those cases, mutations that evolve in
3 rabies viruses may render those viruses able to escape
4 the immune response because the viruses that recognize
5 the -- or I'm sorry -- the antibodies that recognize the
6 virus in the vaccine strain is now distinct from the
7 mutated wild rabies virus.

8 So I would not characterize those mutations
9 as having changed the function. The mutation allowed
10 the virus to escape without change to the function. The
11 virus is still able to infect host cells. The virus is
12 still able to be transmitted to a new host. Those are
13 the key functions of that protein.

14 Those functions are not changed. It's
15 the -- what has changed is the ability of the immune
16 system to recognize and neutralize that virus.

17 Q. Okay. Do you agree that you how you define
18 function matters in terms of understanding what the
19 impact of a single amino acid change will be?

20 MS. LO: Objection, vague.

21 A. I would answer your vague question with a
22 vague answer, which is that definitions always matter.

23 BY MS. LOUGHRAN:

24 Q. And so depending on how you define
25 "function" or what you're looking at in terms of

1 function here, you're saying whether the virus will be
2 recognized by an antibody, that can impact whether you
3 conclude that an amino acid change has an impact on a
4 particular protein; right?

5 MS. LO: Objection to form.

6 A. I would answer by saying, again,
7 definitions matter. And if we're talking about the
8 function of the protein that's mutated -- and that's the
9 rabies virus glycoprotein -- the functions that we know
10 about for that glycoprotein are the ability to attach to
11 and allow -- attach to a receptor on the host cell and
12 allow the rabies virus to invade that host cell.

13 The function of that protein doesn't really
14 have anything do with the host response. So, you know,
15 I don't really see this as a semantic issue. You know,
16 function is a function. But what you're calling out is
17 an altered property, not an altered function.

18 Q. If you look at, for example -- so for
19 example, 24, paragraph 24 of your declaration.

20 A. IPR declaration; correct?

21 Q. Yes. Yes.

22 And I believe you make the same statement
23 in your PGR declaration.

24 You say, "By December 2013, it was clear
25 that Factor C was highly conserved and functionally

1 identical across these species," the four species that
2 are -- the three species listed above in that paragraph.

3 When you say "functionally identical," how
4 are you defining that phrase?

5 A. Well, primarily in the 1980s, and I believe
6 it continued into the 1990s, these proteins were
7 individually purified from the different crab species,
8 and they were extensively studied for their activity.

9 You know, the activity that investigators
10 care about and the pharmaceutical industry cares about
11 is the activity related to detection of endotoxin.

12 And by the time we get to, I believe, 2012,
13 the -- certainly the assays from Tachypleus and Limulus
14 were accepted as functionally interchangeable by the
15 pharmaceutical industry, by the pharmacopeias of the US
16 and Europe and Japan, for detection of endotoxin.

17 Q. Okay. So when you say "functionally
18 identical across species," you're saying that the
19 Factor Cs from each of those species can detect
20 endotoxin?

21 A. They can detect endotoxin in a manner that
22 is, again, functionally not distinguishable in the
23 context of an assay.

24 Q. Okay. And you had referred to in your --
25 when we were discussing sort of the evolution of these,

1 you know, changes to function that required for survival
2 of individuals in a species.

3 Do you recall that?

4 A. Yes.

5 Q. Okay. And so is it your opinion that
6 detection of endotoxin of horseshoe crabs, sort of
7 generally, is a feature that is, you know -- that
8 impacts the survival of the horseshoe crab species?

9 A. Yes, absolutely. Horseshoe crabs are, you
10 know, compared to mammals, anyway. They're quite
11 primitive creatures. Their immune system is more
12 primitive than ours, and this is a key component of
13 their innate immune system.

14 So this recognition of endotoxin is based
15 on, for the crabs, recognition of a broad range of
16 bacterial species. So, for example, if the crab shell
17 is breached and bacteria are able to enter the inside of
18 the crab, the crab needs a way to combat that infection
19 or otherwise get killed by the bacteria.

20 So this clotting cascade involving Factor C
21 is essential to combat that broad array of bacterial
22 pathogens.

23 Q. Okay. Is the specific residual activity of
24 the horseshoe crab Factor C in an ion solution, such as
25 sodium citrate, does that have anything to do with the

1 survival of a horseshoe crab?

2 A. I would not ask the question in that
3 manner. I would rephrase your question, if I may, to
4 ask whether those residual activities correlate with any
5 specific activity or specific property of the enzymes
6 that are related to survival.

7 And I would answer that by saying we don't
8 really have enough information to know how those -- how
9 that laboratory defined in vitro property correlates
10 with the real world in vivo properties of those enzymes.
11 We don't know enough.

12 Q. Okay. So sitting here today, you don't
13 know whether the ability of Factor C to detect endotoxin
14 in the, as you say, sort of the laboratory defined
15 correlates of these ion solutions would have anything to
16 do with whether a horseshoe crab would survive in
17 nature?

18 MS. LO: Objection, asked and answered.

19 A. Yeah, I feel like you just asked the same
20 question again using slightly different words.

21 I would again answer by saying, We don't
22 really know how the in vitro behavior of these enzymes
23 correlates with the in vivo properties that are
24 specifically required in that cascade reaction, other
25 than the fact, in both circumstances, the cascades are

1 triggered by LPS, resulting, in the end, in the shell
2 clot reaction if they're using the natural substrate.
3 Clearly, those two things are closely related.

4 As for the finer details of ion solutions,
5 presumably some of them are related because crabs do not
6 live in pure water; they live in ionic solutions. They
7 live in sea water. So there's going to be some kind of
8 relationship. But we don't have enough information to
9 know exactly what that relationship is.

10 BY MS. LOUGHRAN:

11 Q. Okay. When you look at the data that's
12 presented in the '767 application -- we were looking at
13 Figure 7 a bit earlier -- you agree that these horseshoe
14 crab proteins can have -- well, I'm not going to say --
15 well, similar function in terms of the way you use it in
16 your declaration; right?

17 I think you say functionally identical, but
18 we'll say similar function, but have different enzymatic
19 activities; right?

20 MS. LO: Object to the form.

21 A. Can you point me to somewhere in the
22 declaration?

23 BY MS. LOUGHRAN:

24 Q. Sure.

25 You say, "By December 2013, it was clear

1 that Factor C was highly conserved and functionally
2 identical across these species"; right?

3 A. So we're still looking at --

4 Q. Paragraph 24.

5 A. -- paragraph 24?

6 Q. Yeah.

7 A. I did say that and I stand by that, yes.

8 Q. Okay. But you also recognize that -- that
9 the inventors demonstrated that even within the same
10 species, Factor C proteins had different residual
11 activities; right?

12 A. Can you point to specific data that you're
13 referring to?

14 Q. Well, so just looking at Figure 7, the
15 graph that we were looking at earlier, which is on
16 page 26.

17 A. Yes.

18 Q. Okay. If what -- if what I'm looking at
19 there is function of proteins, you would agree that
20 those are not all identical; right?

21 MS. LO: Objection, vague.

22 A. Let me answer that -- I don't think your
23 question was very specific, so I'm just going to tell
24 you what I see here.

25 If you compare the activity of native

1 Factor C protein -- so that's the one that's called out
2 as TAL -- with the recombinant forms, particularly the
3 recombinant forms made in either CHO-DG44 or HEK293, the
4 residual activities are higher of those recombinant
5 forms. And the recombinant forms produced in CHO-DG44
6 and HEK293 are also higher, generally speaking, than the
7 same recombinant Factor C produced in Sf9.

8 BY MS. LOUGHRAN:

9 Q. I guess my question is: How do you
10 reconcile the differences in residual activity -- well,
11 let me strike that.

12 Do you agree that this idea of residual
13 activity is a -- an aspect of function of horseshoe
14 crabs, as you use the term "functionally identical"?

15 MS. LO: Objection to form.

16 BY MS. LOUGHRAN:

17 Q. I'm just trying to understand the
18 relationship between these things.

19 A. Yeah. If you're -- you're describing
20 things in a way that I would not describe them. Your
21 language is fairly subjective there. You know, I would
22 prefer to stick with definitions.

23 And so residual activity is the property in
24 a defined laboratory assay where the activity of
25 Factor C in a specific ion solution is measured versus

1 the activity of that same protein in pure water.

2 Q. And in your opinion as an expert in this
3 case, is that an aspect of the function of those
4 proteins?

5 A. I object to the word "aspect" because it
6 doesn't really have a defined meaning. So if you could
7 ask your question again without using that word, I can
8 answer it.

9 Q. Well, you can't really object to the words
10 that I use and then refuse to answer the question.
11 So...

12 A. I am asking you to ask -- you said at the
13 beginning I can ask you to rephrase the question, so
14 that's what I'm doing.

15 Q. Okay. What is the relationship that you
16 draw between function when you say "functionally
17 identical" in paragraph 24 --

18 A. Uh-huh.

19 Q. -- and this -- this concept of residual
20 activity as something that we're measuring about these
21 proteins?

22 A. I guess I would answer that by saying a
23 POSA would understand that because these enzymes are
24 highly similar across species, that they will behave
25 similarly across species.

1 For the purified proteins, we know that,
2 from decades of work, people studying these cascades,
3 and that's known to the point that different
4 pharmacopeias in the US, Europe, and Japan accept their
5 behavior as functionally equivalent.

6 And for the recombinant proteins, we know
7 that as well, not as many years of experience, but at
8 this point, we know that. A POSA, as of this date,
9 would have understood that for assays where you are
10 measuring Factor C activity or cascade activity in
11 response to LPS stimulation, you would anticipate
12 similar results across species.

13 Q. Okay. You used -- so you used the word
14 "behaved similarly," and then you said "would anticipate
15 similar results across species"; right?

16 A. Yes.

17 Q. Okay. So you're using -- now you're using
18 the term "similar"; right?

19 So it is not your opinion that the activity
20 would be identical across species; right?

21 A. "Identical" is a very strong word, and it's
22 not one that I would use in the absence of direct data.
23 And, frankly, it's a bar that, in science, you can never
24 really achieve.

25 If you have two investigators that perform

1 exactly the same assay with exactly the same reagents,
2 they will get data out the other end that are similar
3 but not identical. This comes down to things as trivial
4 as, you know, pipetting error and things of that nature.

5 So "identical" is a very strong word. It's
6 not one that I tend to use a lot because it is so
7 strong. So I would say -- I would characterize the
8 "similar" I'm talking about as very similar.

9 For the US pharmacopeia, when they -- and
10 the other pharmacopeias, when they say "functionally
11 interchangeable," does that mean that somebody in Japan
12 and somebody in Europe are going to expect an identical
13 result performing the same assay or the same assay with
14 two different species?

15 No, they're not going to get an identical
16 result, but they are going to get a result that
17 functionally means the same thing, yes or no, versus
18 this is contaminated with endotoxin, this is not, with
19 similar to the same thresholds.

20 Q. So two follow-ups to that.

21 You are the one who used the phrase
22 "functionally identical," so that's what I'm trying to
23 understand.

24 What are you -- you just sort of recoiled
25 when I said, Well, not identical in terms of activity.

1 But you used the phrase "functionally identical."

2 A. Functionally identical but that's a little
3 different.

4 MS. LO: I'm going to object to the form of
5 that question.

6 BY MS. LOUGHRAN:

7 Q. If you could just let me finish it.

8 When you use the phrase "functionally
9 identical," which you use many times in this
10 declaration, what are you referring to?

11 A. So "functionally identical," we know that
12 if we're talking about the Factor Cs and the cascades
13 from all of the enzymes. They all do the same thing in
14 the same way. All right.

15 So we're not saying that, you know, put
16 them in an assay and it's going to give you exactly the
17 same number out the end, but they recognize LPS. The
18 recognition of LPS causes activation of the protease.
19 That protease then cleaves a known substrate.

20 And, generally speaking, what we understand
21 is that those particular functions, the recognition of
22 LPS, the triggering of a clotting cascade, yes, those
23 are identical because, you know, functions are kind of
24 big concepts.

25 Q. Okay. I appreciate that answer.

1 So when you say "functionally identical,"
2 you're referring to, for example, what you show here at
3 Figure 1 on page 10, which is the operation of the
4 cascade. That is functionally identical across species?

5 A. The operation of the cascade. And, again,
6 I would come back to the pharmacopeias. They consider
7 these assays functionally identical across species. You
8 can use the TAL assay. You can use the LAL assay.

9 For the purposes of testing, they are the
10 same. They will give you the same kinds of values.
11 They will give you the same yes/nos when you test
12 samples for LPS contamination.

13 Q. Okay. But I think what you are also
14 pointing out is that that does not necessarily mean that
15 across species you will get identical activities; is
16 that correct?

17 A. I would answer the same way that I've
18 answered before. Yes, across species, you're not going
19 to get identical activities. And even across
20 investigators working with exactly the same samples,
21 you're not going to get identical activities.

22 Identity when you're talking about numbers
23 is a threshold that's essentially impossible to meet.

24 Q. One more follow-up question.

25 The pharmacopeial guidelines, when you talk

1 about interchangeability, those are relative to -- or
2 those are arrived at based on calibration of the
3 different -- of the differential species of protein to
4 some standard; right?

5 A. Based on my understanding of the process,
6 that sounds accurate.

7 Q. Okay. So it's not that you would have
8 somebody doing the -- an assay in Japan and the US and
9 they would run the same assay with everything controlled
10 and get the same result; it is that each of those
11 entities run their assay relative to a calibrated
12 standard; right?

13 A. Any time you run an assay, you're running
14 an assay versus a calibrated standard. You know, this
15 will always come down to many, many different factors,
16 including purity of the enzyme and even the age of the
17 kit, lots of variables. So that's the reason that you
18 have calibrated standards that are included with every
19 kit.

20 Numbers that come out the other end of any
21 kind of assay are meaningless without a calibrated
22 standard -- or relative without a calibrated standard.

23 Q. Okay. And so just to be clear on that, I
24 want to hand you a document that's been marked as
25 Exhibit 2062 in the IPR. It's an article by Bolden,

1 et al. It's been premarked.

2 (Exhibit 2062 was introduced to the
3 witness.)

4 BY MS. LOUGHRAN:

5 Q. And I believe you cited this in your
6 declaration.

7 Do you recognize it?

8 A. I do.

9 Q. Okay. And I just want to turn your
10 attention to page 10 of 12, so the last page of text.

11 And at the top there of that first column,
12 and -- yeah, it starts the sentence that says, "LAL
13 reagents across suppliers are not identical, but
14 compendial LAL tests allow interchangeability based on
15 production controls and calibration to a harmonized
16 international standard."

17 Do you see that?

18 A. I do see that.

19 Q. In your declarations when you talk about
20 the interchangeability of proteins, zymogen proteins,
21 between species, you are using "interchangeability" as
22 it's used here, as calibrated to a standard; right?

23 MS. LO: Objection to form.

24 A. I don't know that I would define it that
25 narrowly because we're not talking about the same thing.

1 You know, here they're talking about
2 reagents across suppliers not being identical. Again,
3 this is going to be for a variety of reasons. It comes
4 down to how the supplier prepares the protein, the
5 purity, the concentration that it's supplied at, how
6 long it is between the time of manufacture and the time
7 that the test is actually delivered and used.

8 And it's a little bit of an
9 apples-to-oranges comparison when we're talking about,
10 you know, comparison across species.

11 BY MS. LOUGHRAN:

12 Q. Okay. But in your declaration, you know,
13 you use the word "interchangeable"; right?

14 A. I did use that word, yes.

15 Q. Okay. You used it in reference to some of
16 these pharmacopeial guidelines. So I just want to make
17 sure, when you use that word, "interchangeability," are
18 you using it consistent with how it's described here?

19 MS. LO: Objection to form.

20 A. Well, again, what's being described here is
21 LAL across suppliers and not LAL versus TAL.

22 If you show me some text that specifically
23 calls out LAL versus TAL, then I can tell you if the
24 meanings there are exactly the same as the meanings
25 here.

1 BY MS. LOUGHRAN:

2 Q. Well, okay. But I think this article
3 compares -- you know, if you look at -- for example, if
4 you look at page 5 of 12, these are -- they are making
5 comparisons between, for example, rFC kits from
6 different species; right?

7 A. Uh-huh.

8 Q. And in the beginning that have text, they
9 say, you know, "The recombinant reagents, generally
10 referred to as rFC, are principally and by design
11 comparable in the sense that they contain cloned
12 coagulation Factor C which is present in LAL/TAL."

13 A. Uh-huh.

14 Q. So my understanding -- and you cited this
15 article -- is that the authors are talking about
16 comparisons between species.

17 A. Certainly there they are. And if in the
18 paragraph you called out before, when they say LAL, if
19 they're including TAL in that explicitly, then I agree
20 with those statements.

21 But it's not possible for me to tell in the
22 paragraph that you called out whether that's what they
23 mean or not.

24 Q. When you use the word "interchangeability"
25 in your declaration, are you using it in a way that does

1 not account for the calibration to harmonized
2 international standards that we've been talking about?

3 MS. LO: Objection to form.

4 A. When I call out interchangeability, what I
5 really mean is that, you know, consistent with what
6 different pharmacopeias say, you can use the reagents
7 from the different crabs to get the same result in an
8 endotoxin test assay; that is, they can both measure
9 endotoxin in the same manner and give you the same
10 yes/no answer.

11 BY MS. LOUGHRAN:

12 Q. And just to be clear, when you -- when the
13 pharmacopeial guidelines say you can use reagents from
14 the different crabs to get the same results, those
15 guidelines require harmonization and calibration to an
16 international standard; right?

17 A. You cannot quantitatively compare anything
18 without calibration to a standard. So, in this case,
19 the standard is one that is internationally agreed upon.

20 Q. Okay.

21 MS. LOUGHRAN: I'm going to switch gears,
22 so let's take another quick break.

23 (A break was taken.)

24 BY MS. LOUGHRAN:

25 Q. Hello again, Dr. Schaefer. How are you?

1 A. I'm good.

2 Q. Good. Did you discuss the substance of any
3 of your testimony with Ms. Shon?

4 A. I did not.

5 Q. Now, in your declarations, you talk about
6 some sequence information that you describe was known
7 for *Limulus polyphemus* by October 2013; right?

8 A. Correct.

9 Q. Okay.

10 A. Are we talking about the IPR?

11 Q. The IPR and the PGR.

12 A. Yes.

13 Q. Okay. And I'm specifically referring to
14 the SRA records that were deposited by researchers at
15 the University of Connecticut.

16 Do you recall those?

17 A. I do.

18 Q. Okay. And you've said this earlier, but I
19 understand your testimony is that you would have -- that
20 a POSA in 2013 -- December of 2013 would have understood
21 that the inventors would have been able to do the same
22 analysis to identify the cDNA sequences of LP Factor C.

23 And that's at paragraph 66 of your IPR
24 declaration if you want to refer to it.

25 But my understanding is your testimony is

1 that a person of skill in the art would have gotten to
2 the LP Factor C sequence using this data that was
3 deposited by researchers at Connecticut; is that fair?

4 A. The POSA is aware of what has been
5 published at the time of the priority date, yes.

6 Q. You opine on this in both of your IPR and
7 PGR testimony; right?

8 A. Yes.

9 Q. So the data that exists in the NCBI
10 database with respect to the SRAs that were deposited by
11 the researchers at Yukon is not specific to any
12 particular zymogen protein; right?

13 A. Sorry. Can you repeat the question?

14 Q. Yeah.

15 The deposits by the Yukon researchers was
16 for the entirety of the horseshoe crab genome and not
17 any specific protein; right?

18 A. Correct. These were shotgun sequencing
19 projects, which means that the whole genome was
20 sequenced in a nontargeted manner, so everything is
21 there.

22 Q. Okay. And I believe you testified earlier
23 that you are not aware of any publication of the Limulus
24 polyphemus Factor C sequence specifically by December of
25 2013; right?

1 A. I don't think I said that in exactly those
2 words. I -- what I would say is that there was no
3 assembly of the entire mRNA or of the entire protein
4 coding sequence of Limulus that was published in any
5 peer-reviewed publication or in any other type of
6 publication that was publicly accessible that I know of.

7 However, the components necessary to easily
8 assemble the full sequence were publicly available.

9 Q. Okay. What is your understanding of when
10 the first report or publication of either the entire
11 mRNA or protein coding sequence of Limulus became
12 available?

13 A. I believe those are identified specifically
14 in my declaration. I do not recall the exact dates, but
15 if you can point me to where in the declaration that's
16 called out, I can either agree or disagree with it.

17 Q. Okay. Well, so are you aware of a Ph.D.
18 thesis by Karen McClymont?

19 A. I am, yes.

20 Q. Is that one of the publications of the
21 Limulus polyphemus Factor C sequence that you are aware
22 of?

23 A. It's one of the ones that I'm aware of,
24 yes.

25 Q. Okay. In your view, is that the first

1 publication of Limulus polyphemus Factor C?

2 MS. LO: Objection, form.

3 A. I do not recall that that was the first
4 public disclosure. It was among the ones I called out,
5 yes. It was among the ones that was one of the earlier
6 public disclosures of the complete sequence.

7 BY MS. LOUGHRAN:

8 Q. Okay. And do you recall, also, the
9 inventors -- or two of the three inventors filed a
10 separate patent application that published with Limulus
11 zymogen protein sequence information in it?

12 A. Yes, I do recall that.

13 Q. Okay. And was that also one of the -- what
14 is the phrase that you used -- the earlier public
15 disclosures of the complete sequence?

16 A. Yes.

17 Q. Other than that -- which I think we refer
18 to either as the 498 PCT or it was published in the US
19 as the '629 publication --

20 A. Yes.

21 Q. -- or McClymont, are you aware of any other
22 earlier publications of the complete sequence for
23 Limulus polyphemus for Factor C?

24 A. If we were talking about the assembled
25 complete sequence of Limulus Factor C, either the

1 complete coding sequence or the complete mRNA sequence,
2 in a contiguous manner where someone could go and
3 retrieve that full sequence without having to do any
4 assembly, yes, I agree with that.

5 And I would also, again, state that that
6 does not mean that the information was not out there
7 since before the December 2013 priority date to assemble
8 those same things, the complete mRNA sequence and the
9 complete coding sequence. It is just they have not yet
10 been published in a public disclosure.

11 Q. And just to be clear, because my question
12 was if you were aware of any earlier publications than
13 the '629 or McClymont, you are not; correct?

14 A. I am not aware of any earlier publications
15 that contain that complete mRNA sequence or the complete
16 coding sequence in an assembled form.

17 Q. Thank you.

18 So you point to the data deposited by the
19 Yukon researchers which you contend was published as of
20 October of 2013; right?

21 A. I believe that's the date that's called
22 out.

23 Q. Okay. And do you -- is your opinion that
24 that is because on the website screen captures, the date
25 October 2013 appears?

1 A. If that date appears at that spot, I would
2 imagine that was the reason that that date was selected.

3 Q. Okay. And it's not a memory test, so
4 just -- so this has been premarked as Exhibit 2053.

5 I'll hand you a copy.

6 And do you recognize this document?

7 A. Yes.

8 (Exhibit 2053 was introduced to the
9 witness.)

10 BY MS. LOUGHRAN:

11 Q. Okay. And what is this?

12 A. This is the Sequence Read Archive of the
13 horseshoe crab transcriptome and the one deposited by
14 the University of Connecticut.

15 Q. Okay. And I think if you -- yeah, so on
16 the front page, there is a Run SRR610305.

17 Do you see that?

18 A. I do.

19 Q. And it says it's published October 31st,
20 2013.

21 Do you see that?

22 A. I do see that.

23 Q. So is that what you were relying on when
24 you put in your declaration that this sequence
25 information was publicly available as of October 31st,

1 2013?

2 A. Those dates agree. So yes.

3 Q. Okay. Did you speak with anybody at the
4 National Library of Medicine to verify that date?

5 A. I took the date at face value because it
6 was published.

7 Q. Okay. But did you do you anything to
8 verify that these actual reads were, in fact, published
9 on that date in 2013?

10 A. I did not myself. I cannot speak for the
11 legal team.

12 Q. Okay. And you didn't yourself run a search
13 for this information as of, say, November 1st, 2013?

14 A. No, I did not.

15 Q. Okay. So your testimony is that a person
16 of skill in the art could take the -- these short reads
17 and assemble them into the Limulus polyphemus Factor C
18 sequences; right?

19 A. They could assemble them into either --
20 well, based on the work that I did, they could assemble
21 them into the nearly complete Factor C. There was a gap
22 in the middle that was not covered by a good quality
23 sequence read. But it would be trivial to fill in that
24 gap by PCR methodology.

25 Q. Okay.

1 A. So certainly, between this sequence deposit
2 and assembling the sequences from that deposit and
3 following up with PCR, both to fill in that gap and then
4 to confirm everything, you could quickly assemble the
5 full Factor C from Limulus.

6 Q. Okay. And you did a BLAST analysis --

7 A. Yes.

8 Q. -- in order to determine this?

9 A. Yes.

10 Q. Okay. And the -- I think you include a
11 figure on page 30 of your declaration of that -- that
12 BLAST analysis.

13 Is that what you're referring to?

14 A. It's a graphical summary, but yes.

15 Q. Okay. So the area sort of between 400 and
16 600, that's the gap area that you're referring to?

17 A. There's a small gap in that region, yes.

18 Q. Okay. And did you actually carry out the
19 procedures that you describe in order -- that a POSA
20 would have done to fill that gap in?

21 A. You mean did I actually obtain some
22 horseshoe crab cDNA and perform PCR to fill in the gap?

23 Q. Yes.

24 A. No, I did not do that, and I don't see any
25 reason why I would need to do that to know that it's

1 possible. I've done many equivalent types of PCRs in my
2 career as a scientist to fill in missing information
3 when you have partial information from a cDNA clone.

4 Q. You've never done PCR on horseshoe crab
5 zymogen proteins; right?

6 A. I've never done PCR on horseshoe crab
7 zymogen proteins. Again, to be familiar with what you
8 need to do to accomplish the procedures that I'm talking
9 about, there is no necessity to have worked on those
10 particular proteins from that particular species. These
11 are species and protein agnostic techniques.

12 This is molecular biology. We are talking
13 about the same nucleotides assembled into the same
14 polymers; that is, DNA and RNA. It doesn't matter if
15 you're talking about a virus, a bacterium, an arachnid,
16 a mammal, a bird; it's all the same.

17 Q. Okay. Did you -- and so you actually
18 created a near-complete sequence of Factor C based on
19 these SR reads; right?

20 A. That is correct. The sequence is nearly
21 complete.

22 Q. Okay. You did that for Factors B and
23 proclotting enzyme as well?

24 A. The same type analysis was performed for
25 Factor B and for proclotting enzyme, yes.

1 Q. Which variant of each of those proteins did
2 you assemble?

3 A. Well, I used tblastn, which requires
4 starting with a protein to query the nucleotide
5 sequence. So I used the complete coding sequence from
6 the Tachypleus Factor C, Factor B, and proclotting
7 enzyme as the probe sequence. So what I assembled was
8 the equivalent of those.

9 Q. Okay. But let me ask again: Which variant
10 of each of the proteins Factor C, Factor B, and
11 proclotting enzyme did you assemble?

12 A. I do not recall other than I started with
13 the Tachypleus full sequences. And off the top of my
14 head, I don't remember whether the Tachypleus full
15 coding sequences -- the protein sequences came from the
16 author's patent materials or from NCBI deposits. So I
17 do not remember which specific variant was used.

18 Q. Are you aware that there are two Factor C
19 variants for Limulus polyphemus?

20 A. I believe I have seen that indicated in
21 either a publication or a database somewhere, but I
22 don't have a strong recollection.

23 Q. Do you have any awareness of whether both
24 of those variants are equally functional?

25 A. I have not looked into the variants of

1 Factor C. I believe there is one specific Factor C that
2 is considered the equivalent of what is used in the
3 nonrecombinant assay, but I have not looked in depth at
4 the reported variant.

5 Q. Okay. So of the two Factor C variants for
6 Limulus polyphemus, you did not try to assemble one or
7 the other; right?

8 A. I did not have a goal of assembling one or
9 another variant. What my goal was to assemble the
10 equivalent of the Tachypleus protein in -- using the
11 Limulus database with the understanding that this would
12 be the same enzyme that is used in the native assay.

13 Q. Would your answer be the same with respect
14 to the four Factor B variants; you did not seek to
15 reproduce any of those four Factor B variants
16 specifically --

17 MS. LO: Object to form.

18 BY MS. LOUGHRAN:

19 Q. -- for Limulus polyphemus?

20 A. So I will give a preamble in that for just
21 about any gene you can identify that has been studied
22 intensely, there are usually a number of different
23 variants that are reported. Often these are splicing
24 variants of one form or another.

25 In most cases, there is zero evidence that

1 the alternative -- those are air quotes in case you need
2 to write that down -- that the alternative forms are
3 actually expressed.

4 So it's -- it ends up often being a waste
5 of time to look at every single possible variant and
6 decide which one you're going to use.

7 What I focused on is what is well
8 characterized and described for Tachypleus, pulling out
9 the transcript that has an open reading frame that
10 corresponds to that enzyme.

11 Q. So you created the sequence based on
12 Tachypleus -- the Tachypleus sequence.

13 You created the Limulus polyphemus based on
14 the Tachypleus sequence; right?

15 A. Based on the Tachypleus protein sequence.
16 And this was tblastn, which will take the protein
17 sequence and identify the cDNA sequence that is most
18 equivalent to that, yes.

19 Q. But then you compared what you got to the
20 Tachypleus sequence that you used to assemble it;
21 correct?

22 A. Correct.

23 Q. You did not account for any other variants
24 of those protein sequences; right?

25 A. It did not seem a good use of my time to

1 look at reported sequence variants that are probably
2 irrelevant with respect to these claims.

3 Q. With respect to the short reads in this
4 database, is there any way to know which short read is
5 associated with which variant?

6 A. Again, these are short reads, as you say;
7 and so all you know about the short read is that it came
8 from an expressed mRNA.

9 The mRNAs are reverse transcribed into
10 cDNA, and what you get is what you get. So with respect
11 to mapping anything back to a particular variant, you
12 know, unless you are looking for a particular exon-exon
13 junction that is characteristic of one variant versus
14 another, there is no way to know which variant it came
15 from.

16 Q. And just to be clear, a POSA in 2013 would
17 have had no way to know which SRA read came from which
18 variant; right?

19 A. A POSA in 2013 would have no way to know
20 which variant it came from. And a POSA in 2013 likely
21 would not have cared which variant it came from. A POSA
22 in 2013 would be looking to assemble the coding
23 equivalent of the Tachypleus Factor C.

24 Q. Doctor, where is the sequence that you
25 arrived at from your analysis in this declaration?

1 A. I don't believe that we actually assembled
2 a sequence and included that in these exhibits. The
3 point of these figures was to show that it is easily
4 possible to assemble a sequence.

5 And, furthermore, you would not use the
6 assembled sequence as your final product; you would use
7 your assembled sequence to design PCR primers that you
8 could be relatively certain are completely correct; that
9 is, they agree very, very well with the Tachypleus
10 sequence.

11 You would then use those in PCR reactions
12 to amplify from your own aliquot of cDNA from this
13 organism. And then you would use those PCR-derived
14 sequences retro from at least two independent PCRs to
15 then assemble the clone.

16 So that's a long way of saying that
17 assembling this collection of reads into a single clone
18 doesn't really serve any value because that's not --
19 that's not the product you would move forward with.
20 It's a source of information that gives you, with some
21 degree of certainty, what the transcript looks like.

22 But then that has to be confirmed with PCR,
23 for the very reason that you mentioned. There could be
24 reported variants and unreported variants that may
25 differ to some degree from what you assemble from these

1 little pieces.

2 Q. Okay. So earlier we talked about how the
3 '767 application that the inventors filed in 2013 has
4 actual cDNA and amino acid sequences for Tachypleus and
5 Carcinoscorpius; right?

6 A. Yes.

7 Q. You did your analysis, but you still did
8 not create sequences like that for Limulus polyphemus;
9 right?

10 A. I did not create assembled sequences like
11 that, because in order to create the types of assembled
12 sequences, I would actually have to do some bench
13 science, and there's not a compelling reason to do that.

14 I went through the initial steps a POSA
15 would go through, and I described that the follow-up
16 steps that a POSA would do to arrive at the kinds of
17 clones that could then be used to make the protein that
18 would be used in the assay; boilerplate steps, simple
19 methodology that can be completed fairly quickly.

20 And, yeah, there's no reason to go through
21 the motions to prove that it was possible. A POSA would
22 understand that all this is possible and doable in a
23 short period of time.

24 Q. And you recognize that the inventors
25 several years later characterized everything that you

1 said there as their invention; right?

2 MS. LO: Objection to form.

3 A. The inventors submitted some later patents,
4 which were continuations of their earlier patents.

5 BY MS. LOUGHRAN:

6 Q. In which they said that they invented
7 recombinant Limulus polyphemus Factor C and included the
8 sequence that they arrived at; right?

9 MS. LO: Objection, form.

10 A. The inventors said a lot of things. I
11 think what is important is the inventors had a number of
12 claims that trace their way back to the original patent
13 application and that original priority date of
14 December 2013.

15 BY MS. LOUGHRAN:

16 Q. Well, the 498 PCT that we've been talking
17 about does not trace back to 2013.

18 Are you aware of that?

19 A. Does it -- it does not trace -- perhaps
20 does not trace directly back to 2013, but it includes
21 many references to 2013.

22 I'm not sure I get what you're saying.

23 Q. Well, we'll cut this line of questioning
24 because I'll get there. I don't want to lose train of
25 thought.

1 So if you want to take a look at
2 paragraph 74 of your declaration -- actually, 78.

3 A. Okay.

4 Q. Okay. Now, you detail a whole host of
5 steps that a POSA would have taken to fill in some of
6 the gaps in the sequence that we were just talking
7 about; right?

8 MS. LO: Objection to form.

9 A. I did not particularly describe it that
10 way. I presented a series of alternative strategies
11 that a POSA could use to arrive at the same result.

12 One of those strategies is using the
13 sequence deposition from University of Connecticut as a
14 starting point to gather a -- what we will call a draft
15 of the full sequence that could then be filled in and
16 verified by PCR.

17 Another method would be using the
18 Tachypleus sequence as a source of a probe to probe a
19 lambda phage library that it's made from the cDNA
20 derived from Limulus.

21 And then the other way is a RACE PCR
22 approach where you would take the protein sequence that
23 was disclosed in Tokunaga, I believe in 1991. Those
24 protein sequences are extensive enough that you could
25 design primers to do two things; one being to amplify

1 most of the heavy chain by standard PCR using degenerate
2 primers, and then you could use RACE PCR to get both the
3 5 prime ends and the 3 prime ends.

4 So those are three independent approaches,
5 none of which is dependent upon the other, that a POSA
6 could use to arrive at the same sequence.

7 BY MS. LOUGHRAN:

8 Q. Now, you acknowledge that none of those
9 approaches would be guaranteed to give you the full
10 Factor C sequence for Limulus polyphemus; right?

11 A. I would not acknowledge any such thing.

12 A competent investigator would be able to
13 use any of those approaches to have a very high
14 expectation of success in assembling the full Factor C.

15 That's not only my opinion, that's also the
16 opinion of Dr. Frohman, who was retained by CRL, Charles
17 River, in their opposition to the EP670 patent. He came
18 to exactly the same conclusions, that this would have
19 been straightforward, no reason to expect any
20 difficulties along the way, you know, standard
21 methodology.

22 Q. Do you know what variant Dr. Frohman
23 arrived at from his analysis?

24 A. I do not recall if Dr. Frohman called out a
25 specific variant.

1 Q. Okay. Well, you use -- at paragraph 78,
2 you talk about a POSA, you know, most likely using
3 peptide sequences for 5 prime RACE and 3 prime RACE.
4 And you say, "in order to maximize the probability of
5 success."

6 So I just want to confirm that you
7 acknowledge that success was not guaranteed; right?

8 A. Scientists never speak in absolutes. You
9 never say there's a 100 percent chance of anything.

10 You know, we know from quantum mechanics
11 that there is a defined probability that every oxygen
12 molecule in this room will suddenly end up in that
13 corner of the room. It's possible.

14 Is it likely to happen? No, it's extremely
15 unlikely.

16 So with everything, there's a spectrum of
17 probability, a spectrum of likelihoods, and we never
18 talk about 100 percent.

19 So, yes, you would do things a certain way
20 to maximize the probability of success; that is to make
21 your life easier. You want it to be successful as
22 quickly as possible to get the target sequence as
23 quickly as possible.

24 But, you know, given the great plasticity
25 of PCR, the flexibility of the RACE approach, I am

1 confident that any POSA would get there in a relatively
2 short amount of time. That's not the same as saying
3 100 percent they're going to succeed, but I have a very,
4 very high degree of confidence that they would get
5 there.

6 Q. Now, you consider yourself a POSA; right?

7 A. I do consider myself a POSA under both our
8 definition and Dr. Jain's definition.

9 Q. And the sequences here were deposited in
10 October -- or were published October 31, 2013; right?

11 A. That is the date that's on the sequences;
12 correct.

13 Q. And the priority date for these patents is
14 December 10, 2013; right?

15 A. That is correct.

16 Q. So about six months -- or six weeks later;
17 right?

18 A. That is correct.

19 Q. And so have you done anything to verify
20 that a POSA would be able to assemble the draft
21 sequence, as you call it, and within six weeks, have the
22 full sequence based on the methods that you describe
23 herein?

24 A. Again, I am confident that a POSA would be
25 able to use that information and the methods that I

1 describe to accomplish that task within a few days.

2 I'm also confident that even if a POSA did
3 not have knowledge of that deposition for whatever
4 reason -- and, again, we're assuming that a POSA does
5 have knowledge of that, but let's pretend they don't --
6 that they wouldn't even need that, they could use the
7 sequences published by Tokunaga in 1991 and, again,
8 within a few days, assemble the complete sequence of
9 Factor C.

10 The probing at the lambda phage library
11 would take slightly longer simply because that's a messy
12 technique with a lot of incubation steps and a lot of
13 phage amplification steps. I've done it before. It's
14 slow, it's clunky; it's not the one I favor, but it's
15 very doable. It takes a little longer. Even there, a
16 few weeks.

17 Q. So then you did do a comparison between
18 Limulus polyphemus Factor C, B, and proclotting enzyme,
19 and the other two species, Carcinoscorpius and
20 Tachypleus; right?

21 A. If you're talking about the BLAST
22 comparison, yes, that is what was done. I'm not sure
23 exactly what you're referring to.

24 Q. Well, I'll hand you the exhibit.

25 Can you -- or, actually, this is already

1 marked as Exhibit 2081.

2 A. Clustal alignment, yes.

3 (Exhibit 2081 was introduced to the
4 witness.)

5 BY MS. LOUGHRAN:

6 Q. Okay. So do you recognize this document?

7 A. I do recognize this document.

8 Q. Okay. And so what is this?

9 A. You're asking me to describe the document?

10 Q. What is this document? Yeah.

11 A. Okay. So this is a Clustal alignment of
12 the protein sequences from three crab species: Limulus,
13 Carcinoscorpius, Tachypleus.

14 And what is done here is the algorithm
15 shows the degree of conservation at each amino acid,
16 with the asterisk indicating fully conserved, the two
17 dots indicating conservation between groups with
18 strongly similar properties, and the one dot indicating
19 conservation between groups with weakly similar
20 properties. The space underneath this blank, those are
21 considered nonconserved.

22 Q. Okay.

23 A. The sequence has then been annotated to
24 show the location of all the sites that were flagged by
25 the algorithm as being nonconserved.

1 So the case where green is shown, that is
2 where there is a residue flag that is nonconserved that
3 is only nonconserved between Limulus and one of the two
4 other species.

5 So if we look down -- let's go four lines
6 down. The first time this happens, there's methionine
7 and Limulus, there's lysine and Tachypleus, but it's
8 marked with green because there's also methionine and
9 Carcinoscorpius.

10 Where the residues are shaded in red,
11 that's where there's a nonconservative substitution in
12 Limulus that does not appear in either of the two other
13 species.

14 Q. What is the -- where did you -- strike
15 that.

16 For the Limulus sequence that you use here,
17 where did you get that?

18 A. I believe this Limulus sequence came from
19 the inventors' disclosure in the 498. To the best of my
20 memory, that's where that came from.

21 Q. Okay. So this sequence does not come from
22 the University of Connecticut deposits?

23 A. No.

24 Q. Okay. Now the -- if you look at your
25 declaration on page 46, and just -- I'd like to just

1 have it sort of next to the exhibit that you're looking
2 at.

3 A. Sorry. Say it again. Where am I?

4 Q. Page 46.

5 A. Page 46. Yes.

6 Q. Okay. This is the same comparison the
7 one -- the paragraph -- the chart on page 46 has just
8 been color-coded to specify certain regions; correct?

9 A. It's a graphical representation of what is
10 shown in this exhibit but there are some key
11 differences. One, you've pointed out that the
12 functional domains have been color-coded. And the other
13 is that now instead of having the full indication of
14 conservation underneath, all that we've included is the
15 coloring of the nonconservative substitutions.

16 Q. Okay. Looking at Exhibit 2081, did you
17 account for charge differences between amino acids in
18 determining whether something was a conservative or
19 nonconservative mutation?

20 A. This is the exhibit we're talking about?

21 Q. Yes.

22 A. Okay. To be clear, I don't make the calls
23 here; the algorithm makes the calls. And so charge
24 differences are certainly considered by the algorithm.

25 Q. Okay. So just for example, when -- let's

1 see. If you look on the row that is marked -- the end
2 is 180. If you're all the way at the end and you count
3 back to the third-to-last like double-dot, conservation
4 between groups of strongly similar properties.

5 Do you see that?

6 A. Uh-huh.

7 Q. And it shows N for Limulus and D and D for
8 Carcinoscorpius and Tachypleus.

9 Do you see that?

10 A. No. Wait. I'm not seeing where you're
11 talking about.

12 Q. Are you at row 180?

13 A. 180 is here, yes.

14 Q. Yep.

15 And you count back the third double-dot.

16 A. Oh, sorry, third double-dot, yes.

17 Q. Okay. Does the program account for the
18 fact that those differences -- those amino acids have
19 different charges?

20 A. So we have aspartic acid that's compared to
21 the spire gene. They are chemically similar; the major
22 difference is their charge.

23 So, again, the program is an algorithm.

24 And from the point of view of that algorithm, they have
25 strongly similar properties, even though there's a

1 charge difference.

2 Q. Okay. But would the algorithm give you two
3 dots for amino acids where there was no charge
4 difference as well?

5 A. It might; it might not. It depends on the
6 circumstance. You know, again, it's a gestalt that is
7 built into the algorithm. Charge is not the only thing
8 that's considered. Hydrophobicity versus
9 hydrophilicity, the size of the amino acid side chain,
10 the length of the amino acid side chain, all of these
11 are built into the algorithm.

12 I assume that there is an associated score,
13 and I would furthermore assume that each of these
14 designations reflects different thresholds from that
15 scoring system.

16 Q. Okay. You acknowledge that the '767
17 application discusses conservative and nonconservative
18 mutations; right?

19 A. Yes. They have their own set of criteria
20 for listing various amino acid where they consider
21 certain groups of amino acid to be conserved.

22 I don't recall if they had any lists of
23 amino acid where they called out them for being --
24 called them out for being nonconserved, but they
25 certainly had lists of related amino acid that they

1 considered conserved.

2 Q. Okay. And my question to you is: The
3 algorithm that you are relying on for this exhibit, is
4 it consistent with the inventors' disclosure regarding
5 what is a conservative or nonconservative mutation?

6 A. The inventors' disclosure used what I would
7 call a textbook definition and a fairly conservative
8 definition of what amino acids are considered conserved
9 versus nonconserved.

10 I would say that the Clustal algorithm uses
11 a more sophisticated call. So there's both more
12 granularity with the Clustal ranking system versus, you
13 know, simply listing amino acid and saying these are
14 conserved.

15 But, yeah, you know, there's going to be
16 some similarities; there's going to be some differences.
17 For the most part, I would consider that you would come
18 to generally similar conclusions using the Clustal
19 algorithm and the lists of amino acid that the inventors
20 call out, not necessarily identical conclusions.

21 But I think the big overall conclusion
22 would be, hey, look, these proteins are very similar; we
23 find a few differences here and there.

24 Q. When was the version of 1.2.4 Clustal
25 released?

1 A. I don't know about the specific version
2 1.2.4. I know that Clustal Omega itself was available
3 as of the priority date.

4 It can be not that straightforward to find
5 the exact version that was used previously. But for a
6 simple analysis like this, I would be very confident
7 that for what we're talking about here, conserved versus
8 nonconserved, it doesn't matter which version of Clustal
9 Omega you use.

10 I doubt that part of the algorithm has
11 really changed. Usually what they change in the
12 algorithm over time is the ability to successfully align
13 more divergent sequences.

14 These sequences are so similar, I can't
15 imagine that any version of Clustal, even predating
16 Omega -- W was the version that predated Omega. I'm
17 pretty sure that W would have given you exactly these
18 same results as far as conserved versus not conserved
19 residues.

20 Q. Okay. But your testimony is that a person
21 of skill in the art as of 2013 would gather up some
22 information and be able to make some predictions about
23 sequences and their corresponding function?

24 A. Yes. They would use the Clustal algorithm
25 and come up with something not materially different from

1 what we've included as this exhibit.

2 Q. But how do you know that it would not be
3 materially different?

4 A. I've worked with Clustal for decades, and I
5 know -- I have a very good grasp on what changes over
6 time and what does not.

7 You know, the definition of similarity
8 between amino acid, you know, that's something we've
9 known from day one. The authors of the Clustal
10 algorithm would have decided what is similar, what's
11 not, what counts as these threshold measures very early
12 on. I don't see that changing over time.

13 I don't see that being any different to a
14 POSA now versus a POSA in 2012 versus a POSA years
15 earlier than that, from the perspective of what we're
16 talking about right here.

17 Q. But you acknowledge that the POSA reading
18 the specification would review the inventors'
19 definitions of conservative versus nonconservative
20 mutations, which would be different than the Clustal
21 algorithm; right?

22 A. I don't really know what a POSA would look
23 at, you know.

24 Again, this -- if we're talking about that
25 huge patent, I don't know that a POSA would read it from

1 beginning to end.

2 A POSA is likely to use the tools that they
3 are most familiar with and most confident in. They may
4 not pay any attention at all to what the inventors call
5 out as being conserved versus nonconserved. A POSA is
6 going to use the resources that they think are best for
7 carrying out instructions.

8 In this case, the instructions are, you
9 know, conducting the assay and, for what we're talking
10 about here, cloning the Limulus Factor C.

11 Q. Okay. If you look at the figure on
12 page 46, the third row from the bottom.

13 Do you see it starts, "The serine protease
14 domain"?

15 A. Yes.

16 Q. The second one over in that shading, do you
17 see "VWW"?

18 A. Yeah.

19 Q. Is that a conservative or nonconservative
20 mutation?

21 A. It's nonconservative.

22 Q. Okay. You acknowledge that's a
23 nonconservative mutation in a functional domain of this
24 protein; right?

25 A. It's a nonconservative domain --

1 nonconservative mutation in a functional domain. I
2 would point out that this is the second amino acid in a
3 very large domain, which means it's toward the very end
4 of the domain. For that reason alone, a POSA might
5 suspect that it is not functionally significant.

6 And then there is also other analysis that
7 I have included, some 3-dimensional modeling of the
8 Factor C from Limulus and the Factor C from Tachypleus.
9 And in that 3-dimensional modeling done with Phyre, you
10 come up with 3-dimensional models that are essentially
11 indistinguishable.

12 In that particular region, there's no
13 evidence of impact on the predicted structure of the
14 molecule.

15 So, you know, you put just those two
16 results alone together, and a POSA is not likely to
17 expect that that particular mutation would have
18 functional significance.

19 Add to that the fact that these proteins
20 have been biochemically characterized since the 1980s
21 and known not to behave differently in the assay in
22 which you are measuring endotoxin activity.

23 Add all those things together, and a POSA
24 will include that it's very unlikely that that
25 nonconservative mutation has any functional

1 significance.

2 Q. Okay. But, I mean, earlier you did say
3 that in functional domains, a single amino acid change
4 can have an impact on function.

5 So I'm just trying to point out that there
6 is a nonconservative mutation in a functional domain in
7 Factor C; right?

8 A. I am not sure of your meaning in putting
9 those statements together. Again, scientists never
10 speak in absolutes. So, certainly, a single
11 nonconservative mutation can have an impact in a
12 functional domain.

13 For example, if you mutate one of the
14 catalytic amino acid to something nonconservatively, you
15 are going to kill the activity of that enzyme.

16 So we know that there are specific amino
17 acids within a functional domain that are absolutely
18 going to have an impact.

19 And then there are a lot of amino acids in
20 a functional domain where many different amino acids are
21 going to be tolerated, and there will be no functional
22 impact.

23 So can it? Yes. But, again, I've just
24 described at least three distinct pieces of evidence
25 that would argue against that. You know, these are not

1 random mutations. This is a variation between two
2 species of crabs.

3 We're talking about the Factor C protein
4 where both of these proteins have been purified from the
5 crabs and extensively biochemically characterized. And
6 we're aware of no meaningful functional difference
7 between those enzymes.

8 So the most reasonable conclusion is that
9 particular amino acid change is going to have no
10 functional impact.

11 Q. Again, when you say "functional impact,"
12 you mean sort of moving through the cascade to detect
13 endotoxin; right?

14 A. Moving through the cascade to detect
15 endotoxin and functioning as an endotoxin detection
16 reagent in the context that we are familiar with.

17 There's simply no reason to believe that
18 it's going to have a functional impact in any kind of
19 assay where the goal is to measure the activity of an
20 endotoxin.

21 That is what a POSA would understand.

22 Q. Okay. Did you or did the algorithm
23 consider isoelectric points in view of paired cysteine
24 residues in this sequence?

25 A. To my knowledge, that is not a component

1 that the Clustal algorithm will look at because the
2 Clustal algorithm is agnostic to any of those higher
3 order interactions.

4 So while the algorithm can recognize where
5 cysteines are present, the algorithm has not been
6 designed to say this cysteine is paired with that
7 cysteine, et cetera.

8 Q. Did you do that analysis on top of the
9 algorithm or outside of the algorithm?

10 A. That is not a property that I considered in
11 my analysis. And I would add to that, that is not a
12 property that I have seen called out in the patent or
13 any of the patent-related documents; or I don't even
14 recall Dr. Jain discussing that.

15 Q. Now, you reference modeling these proteins,
16 sort of doing a 3-D model of these proteins; right?

17 A. I did.

18 Q. And the model is just an estimate of what
19 you'd see; it's not the actual sort of characterized
20 crystal structure; right?

21 A. I don't know that I would refer to a model
22 as an estimate. The model is just that; it's a model.
23 It's a -- it's a prediction of what the 3-dimensional
24 structure is likely to look like based on sequence
25 feature matches to the database -- database of known

1 structures.

2 And I would add even to that that, you
3 know, a crystal structure is not -- does not represent
4 the full spectrum of confirmations of a protein. It's a
5 preferred confirmation of a protein in whatever state
6 that protein was crystallized.

7 So it gives us a very good idea of a
8 confirmation that that protein can adopt, but it clearly
9 does not represent every confirmation that a protein can
10 adopt. It's a very useful piece of information to tell
11 us something about the domain structure of a protein.

12 Q. Okay. If I can find it --

13 Okay. So I'm going to hand you
14 Exhibit 2100.

15 (Exhibit 2100 was introduced to the
16 witness.)

17 BY MS. LOUGHRAN:

18 Q. And is this the document in which you did
19 your 3-D modeling?

20 A. Yes. This is the output from the Phyre 2.2
21 server.

22 Q. Now in paragraph 98 of your declaration,
23 you say you got this by comparing the predicted
24 3-dimensional structures of Limulus and Tachypleus based
25 on template c9ekeD.

1 Do you see that?

2 A. Yes.

3 Q. Okay. So what is template c9ekeD?

4 A. So if we look at the Phyre 2 output -- so
5 all of these designators -- let me back up a step.

6 So we have -- Phyre will create a list of
7 matches where your structure is compared to everything
8 that's out there in the protein database, in the crystal
9 database, and then it will create a rank-ordered list.
10 And the rank-ordered list simply reflects the best fit.

11 So c9ekeD was the best fit, and that is a
12 crystal structure from complement C1r subcomponent.

13 Q. Okay. So you're -- when you look at your
14 comparison here, you're basically comparing -- well,
15 again, the Limulus sequence here that you're using is
16 from the inventors' disclosure; is that right?

17 A. I believe that is correct.

18 Q. And you're comparing it to a model which
19 has already been determined to be the best fit for
20 that --

21 A. What do you mean "already determined"?

22 Q. Well, you got to the model -- you just said
23 you got to the model as the model being the highest
24 scoring model for both Tachypleus and Limulus
25 polyphemus.

1 A. Yes.

2 Q. So you're comparing the Limulus sequence to
3 something that's already been determined to be very
4 similar to the Limulus sequence; right?

5 A. I don't know that anybody else has run this
6 analysis. So the way the analysis works is you input
7 your sequence, and the algorithm, the Phyre 2.2
8 algorithm, compares that sequence and its features to
9 everything that's been crystallized. And then based on
10 the calculations that the algorithm performs, it will
11 give you a ranked scoring system.

12 So I did the same type of analysis for both
13 Limulus and for Tachypleus. And what came out the other
14 end was rank-ordered lists for both. And in both cases,
15 c9ekeD was the top-scoring model for both of them
16 independently.

17 Q. Did you compare the predicted sequence of
18 Limulus polyphemus to Tachypleus?

19 A. Are you asking -- that's a very vague and
20 open-ended question. Can you make it more specific?

21 Q. Sure.

22 I am just trying to understand, in your
23 testimony, you're saying that you compared the predicted
24 3-dimensional structures of Limulus polyphemus and
25 Tachypleus to a model.

1 I'm just asking if you compared them to
2 each other.

3 A. Yes. The two models that come out the
4 other end are compared to each other on the final page,
5 707. So I show the Tachypleus model on the left, the
6 Limulus in the middle, and then the overlay of the two
7 on the right side. So that's where the two of them are
8 compared.

9 So if you superficially just look at the
10 two, it's very hard to see any differences between them.
11 And that's further emphasized in the overlay where one
12 is red and one is blue. If there's any differences at
13 all, they're quite subtle.

14 Q. Just so that I'm clear, when you have -- on
15 the left side, this picture, Tachypleus tridentatus
16 Factor C --

17 A. Yes.

18 Q. -- is that the predicted 3-D structure of
19 Tachypleus tridentatus from its sequence or from its
20 sequence compared to this model?

21 A. I don't think there's a distinction between
22 the two things you have said.

23 Again, you input the sequence into this
24 program which uses an algorithm to compare the sequence
25 to every crystal structure that's ever been done. It

1 finds the best fit based on, you know, comparing many
2 parameters of the sequence that influence secondary and
3 tertiary structure. And it will come up with a model
4 based on those prior crystal structures.

5 And so in this case, we're looking at the
6 models that are predicted based on comparison to the
7 crystal structure c9ekeD.

8 Q. So the one on the right here, the
9 alignment, that's an alignment of model comparison
10 versus model comparison; right?

11 A. Correct.

12 Q. Okay.

13 A. The two models are overlaid.

14 Q. Got it.

15 A. So the expectation is that if one model
16 predicts a structure that is somewhat different than the
17 other model, when you overlay the two, that will be much
18 more clear because you can see where the two don't
19 align.

20 Q. Understood.

21 When you put these into Phyre, you -- on
22 the front page, it says 35 percent of your sequence have
23 been molded.

24 Do you see that?

25 A. Yes.

1 Q. So only about a third of the Factor C
2 protein ends up getting modeled here; right?

3 A. Factor C is a very big protein that has a
4 number of different functional domains. So what this
5 means is that there is not another protein in the
6 database that has that same series of functional domains
7 spaced in the same way. The algorithm can only model
8 versus what's already in the database.

9 So it found proteins in the database that
10 are very similar to the catalytic domain, which is, you
11 know, the domain -- we'll call it the business end of
12 the molecule. That's the part that actually performs
13 the protease function, arguably the most important part
14 of the molecule, and the two next upstream CCP domains.

15 So, yes, not the entire thing, but that's
16 the most that it could do based on the existing
17 structures in the database.

18 Q. Okay. And are the existing structures that
19 got compared in this model when you ran it the same as
20 the ones that would have existed in 2013?

21 A. I did not rigorously analyze that. You
22 know, there's a large number of models here that are
23 high-scoring, so I would say -- I would be pretty
24 confident that many of them would have already been in
25 the database, but I don't know if they were all there.

1 Q. Okay. So you did this in 2025; right?

2 A. Yes.

3 Q. So about 12 years later; right?

4 A. Yes.

5 Q. You agree --

6 A. And crystallizing proteins for a long time,
7 though.

8 Q. Right.

9 But you agree that the existing
10 crystallized structures in the database as of 2025 would
11 be different than those that would have existed in the
12 database as of 2013; right?

13 A. There would be different structures, you
14 know, given the fact that the confidence levels of the
15 top scorers here: 100 percent, 99.8, 99.4, 99.9, 99.9,
16 and then it goes on for quite some time in that regard,
17 I don't think you would have come up with results that
18 are meaningfully different.

19 Q. But, again, even these confidence intervals
20 are calculated as of 2025, not 2013; right?

21 A. Phyre has been around since before the
22 priority date. I don't see why the confidence scores
23 would have been different. If the structure was in the
24 database at the time, which I'm fairly confident that at
25 least some of these were, then I don't think the

1 confidence scores would have been any different.

2 MS. LO: Counsel, we've been going for a
3 while.

4 MS. LOUGHRAN: Sure. Should we take a
5 lunch break?

6 Go off the record.

7 (A lunch break was taken.)

8 BY MS. LOUGHRAN:

9 Q. Good afternoon, Dr. Schaefer. Welcome
10 back.

11 A. Thank you.

12 Q. Did you discuss any of your testimony this
13 morning over the lunch break with Ms. Lo?

14 A. No.

15 Q. Okay. So you've referenced today and you
16 reference in both of your declarations an article that I
17 think we commonly call Tokunaga.

18 Do you know that article?

19 A. Yes, I do.

20 (Exhibit 1022 was introduced to the
21 witness.)

22 BY MS. LOUGHRAN:

23 Q. Okay. I'm just going to hand you a copy of
24 it because I have some questions. So this has been
25 marked as Exhibit 1022 in the IPR. It's also cited in

1 the PGR. And it is the Tokunaga 1991 reference.

2 Do you see that in front of you?

3 A. I do.

4 Q. Okay. Now, Tokunaga doesn't talk at all
5 about recombinant proteins; right?

6 A. Correct.

7 Q. And it doesn't talk about the residual
8 activity parameter, either; right?

9 A. I don't recall seeing any discussion of
10 residual activity, no.

11 Q. Okay. Doesn't -- Tokunaga doesn't discuss
12 whether the proteins studied have any particular ability
13 to resist ion inhibition; correct?

14 A. Tokunaga is mostly discussing biochemical
15 and immunological characterization of the Limulus
16 enzyme. And this was 1991 while what we had to work
17 with were the purified proteins. So this is really a
18 biochemistry study of the proteins. So concepts like
19 residual activity are not discussed in this publication.

20 Q. Okay. And so when you say -- great.

21 So Tokunaga discusses the naturally
22 occurring Factor C proteins; right?

23 A. Naturally occurring Factor C proteins
24 purified from the crab blood, essentially, yes.

25 Q. Okay. Now, in your declaration -- your

1 '318 declaration at, let's see, I think paragraph 61.

2 Hold on.

3 Yes, paragraph 61, you write, "As known in
4 the art before 2013, the individual amino acid
5 compositions of the two proteins, Tachypleus and
6 Limulus, and of their chain unit -- subunits were
7 indistinguishable."

8 Do you see that?

9 A. That is quoted text from Tokunaga, yes.

10 Q. Yes.

11 And that's based -- in this text, that's
12 based on the compositions that are shown in, for
13 example, Supplementary Table 2 on page 156?

14 A. Yes.

15 Q. Okay. And so what is shown here in
16 Supplementary Table 2 is the sort of residue count for
17 each of those amino acid; is that correct?

18 A. That is correct.

19 Q. Okay. So, for example, if you look at the
20 second one down, Thr, is that threonine?

21 A. Threonine.

22 Q. So the 53.6 is the residue count for that
23 amino acid for Limulus; is that right?

24 A. Yes.

25 Q. Relative to 59 is the residue count for

1 that amino acid in Tachypleus; is that right?

2 A. Correct.

3 Q. Okay. And then as you see at the bottom,
4 they total all those up. And so it looks like with
5 respect to the whole chain for Factor C, at least the
6 ones that are counted here, there are 920.4 for Limulus
7 and 994 for Tachypleus; right?

8 A. That's what this analysis shows, yes.

9 Q. Okay. So they are different; right?

10 A. Well, in this assay, they're different. I
11 think there is somewhere else in the publication where
12 they come up with a more exact count for the amino acid,
13 unless I'm confusing with another publication. But I
14 think they did come up with a more exact number.

15 But, anyway, it's -- in that particular
16 table, it's measured, which ends up being an estimate
17 based on biochemistry versus known, in the parentheses.

18 Q. So at least with respect to the
19 measurements took that are reflect in this table, there
20 are differences between the amino acid counts shown here
21 as between Limulus and Tachypleus; right?

22 A. With the caveat that a POSA knows that
23 these are not exact counts. I mean, there's decimals;
24 right?

25 920.4, you won't have .4 of amino acid.

1 Clearly these are numbers based on a biochemical
2 analysis. And the conclusion that a POSA would draw is,
3 oh, look, in these many respects, they're very similar,
4 both in the total of amino acid and in the individual
5 amino acid composition. And for, you know, 1991
6 biochemistry, this is pretty solid.

7 Q. Okay. But, again, I'm just asking you that
8 with respect to the reports in this assay, the amino
9 acid compositions between Limulus and Tachypleus are
10 different.

11 You agree with that; right?

12 MS. LO: Objection to form.

13 A. In this table, there are some differences.
14 You know, we can say that 920.4 and 994 are not the same
15 number.

16 Again, I will emphasize that a POSA would
17 not consider that the take-home message of the data.

18 What a POSA would focus on, given the type
19 of assay that this is, they use the very many
20 similarities, and they are not going to take away from
21 this that what is being represented here is the final
22 exact total for Limulus because it is based on a
23 biochemical assay in an amino acid-by-amino acid manner.

24 So, particularly, when you get to the point
25 of adding up all these amino acids, that's going to

1 amplify the error that's inherent in the assay to start
2 with.

3 So this is not a particularly good assay
4 for accurately determining the exact length of the
5 enzyme, which we know from later work, because they only
6 differ by a single amino acid.

7 BY MS. LOUGHRAN:

8 Q. Okay. Now, I understand that you want to
9 explain away differences, but I do need an answer to the
10 question, which is just: In this table, are the amino
11 acid compositions, as reported between Limulus and
12 Tachypleus, different?

13 MS. LO: Objection to form, asked and
14 answered.

15 A. Yes. I believe I answered that very
16 specifically. If you look at the two numbers that are
17 next to the word "total," you have 920.4 for Limulus and
18 you have 994 for Tachypleus; the 920.4 being estimated
19 and the 994 being actual.

20 And, again, estimate versus actual, I do
21 agree they are not the same number. I just disagree
22 with what you were trying to construe the intention of
23 this data is.

24 BY MS. LOUGHRAN:

25 Q. Okay. Thank you.

1 And then Tokunaga does some partial amino
2 acid sequencing, which is shown in Figure 7S; right?

3 A. Correct.

4 Q. And what's shown there in boxes are the
5 amino acid residues that are the same between Limulus
6 polyphemus; right?

7 A. Correct.

8 Q. And then the ones that are not in boxes are
9 the amino acid residues that are not the same between
10 Limulus and Tachypleus; right?

11 A. Correct.

12 Q. Okay. Now, the -- but this is only a
13 partial sequence. Factor C is much larger than what's
14 shown here; right?

15 A. Correct. They were using a technique that
16 will give you protein sequence starting at N-free
17 N-terminus, and you can only go so far with that
18 technique, dependent upon a number of factors.

19 So what we are so seeing here is N-terminal
20 sequence for the heavy chain, N-terminal sequence for
21 the common light and A chain, and N-terminal sequence
22 for the B chain.

23 Q. Okay. Sorry. My pen just ran out.

24 Okay. And I think you said -- did you
25 refer to Tokunaga's method for sequencing here as a

1 tryptic method?

2 A. I might have said tryptic before, but this
3 is end degradation. Tryptic is usually a precursor to
4 that. And you take a full-length protein, you chop it
5 up with trypsin and then you sequence from the
6 N-terminal ends that you generate.

7 They actually didn't do that here, because
8 they have N-terminal ends from the natural cleavage
9 sites. So if I said tryptic before, I misspoke. It's
10 end degradation that they're doing here or some
11 variation of that.

12 Q. Now, the amino acid sequences, as reported
13 in 7S, those sequences are different sequences for
14 Limulus versus Tachypleus; right?

15 A. I'm not sure what you're asking there.

16 Q. Well, the -- for example, let's just take
17 the B chain. The amino acid sequence for Tachypleus and
18 the amino acid sequence for Limulus, at least from this
19 partial sequence, are not the same; right?

20 A. What is shown here is not identical. There
21 are -- as you have said, there are regions of identify
22 that are boxed, and any other amino acids that are shown
23 is nonidentical.

24 Q. Okay. You agree that, as reported in
25 Tokunaga, Limulus -- the Limulus sequence is missing an

1 end glycosylation site relative to Tachypleus; right?

2 A. I do not completely agree with that
3 statement. So for the most part, the N-terminal peptide
4 sequencing shown in Tokunaga is of very good quality.
5 That quality is not as good for B chain. And if you
6 compare to the actual sequence that was determined
7 later, the three final residues that they've determined
8 there, LGL, were actually incorrect. Everything else is
9 correct.

10 But the correct is actually NST, that that
11 glycosylation site is actually identical and it is
12 conserved between the species.

13 So those data in this supplemental figure
14 were not 100 percent accurate.

15 Q. But if I was a POSA reading Tokunaga, I
16 would understand that Limulus has a different -- is
17 missing a glycosylation site relative to Tachypleus;
18 right?

19 A. I think if you were a POSA reading
20 Tokunaga, you would take those data with a grain of
21 salt, because there is such high divergence there,
22 actually, that all three of those are fairly
23 nonconservative substitutions. ^ Start

24 You have a NIS paragene [ph] substituted
25 with a leucine. Leucine is very hydrophobic. Then you

1 have a glycine, then you have a leucine. That's three
2 hydrophobic residues in a row, versus NST, which is very
3 hydrophilic. So a POSA would look at that and say,
4 well, I don't know about the end of that sequence. And
5 also it's very short, which would also give you pause.

6 So I think a POSA would focus more on the
7 heavy chain and the light chain sequences, which both
8 match better, they're longer, so they're clearly of
9 better quality.

10 Q. Do you recognize that the -- in the B
11 chain, that there is a residue distinction or a mutation
12 between the W and the V right before the NGN?

13 A. Yes. In the first four amino acid, there's
14 one nonconservative substitution. I do recognize that.

15 Q. And that's right before the cleavage site;
16 right?

17 A. It's in the vicinity of the cleavage site.

18 Q. Do you -- okay. And when you did your --
19 your modeling with Phyre, did you account for that amino
20 acid difference and what implication it would have on
21 that cleavage site?

22 A. I am not sure what question you are asking.

23 Q. Well, did you look -- in your model, did
24 you zoom into the cleavage site to look and see, for
25 example, what having one amino acid versus the other

1 would do to the structure of the molecule?

2 A. I did look at polymorphisms that were in
3 functional domains to see if there were any appreciable
4 differences.

5 I would like to look back at the
6 color-coded alignment to make sure we're talking about
7 the same thing that I am thinking. Do you know off the
8 top of your head what page that was on? That would be
9 helpful.

10 Yes. So that is the same substitution that
11 is shown as being at the very beginning of the serine
12 protease domain. And yes, I looked very carefully at
13 that region of the molecule. And in my inspection of
14 it, I didn't see any clear difference in the structures.

15 Q. Are you aware that the -- I think the V --
16 or the W, which is tryptophan, is a much bulkier residue
17 than phalein?

18 A. Yes, it's a bulkier residue. I agree with
19 that.

20 Q. So you agree that would be reflected in the
21 protein structure; right?

22 A. Certainly, if you look down to the level of
23 side chains, you will see a bulkier residue there. The
24 way the Phyre structures are compared, we're really
25 looking at the backbones. We're not looking at the

1 filled-in model, where you also see the side chains.

2 And what we're looking for is deviations in that

3 backbone structure.

4 So is there a loop that's been moved over
5 here, or a loop that's not there, and it's now an alpha
6 helix instead, things of that nature. And from my
7 inspection of the Phyre structure, I did not see any
8 movements in the predicted backbones for Limulus versus
9 Tachypleus with that model.

10 Q. Okay. But do you acknowledge that having a
11 bulkier residue at that position in the serine protease
12 domain right before the cleavage site could have an
13 impact on cleavage?

14 A. That sounds like a question where you are
15 asking me to speculate. Again, I will come back to the
16 principle of being a scientist and saying could be.

17 You know, given that we know that the
18 activation of these proteases are dependent on those
19 cleavage events and reflective of the activity of the
20 enzymes, and that, you know, overall, the functions of
21 these molecules are remarkably equivalent between
22 species, I would again say that the burden of the
23 evidence says that there's no effect there.

24 These enzymes activate in a very equivalent
25 way, which argues that that cleavage event occurs in a

1 very equivalent way with an equivalent efficiency.

2 Q. Can we agree that knowing whether or not
3 that amino acid substitution would have an impact on
4 cleavage would be an unknown to a POSA looking at this
5 information at the time, as of 2013?

6 A. Well, again, a POSA would consider
7 everything that's known about Limulus Factor C. This is
8 not an unknown protein. It's not an unknown structure
9 function relationship.

10 By this time, you know, even though we
11 are -- we're talking about the early 1990s, there had
12 been fairly extensive biochemical characterization done,
13 including in this paper itself, and in the prior paper.
14 I think it was -- Muto was the first author. So there
15 had been some pretty extensive biochemical
16 characterization done.

17 We knew about the cleavage sites. And, you
18 know, considering all of the data in Tokunaga, and
19 Tokunaga himself even says something very specific about
20 the functional equivalent of these enzymes -- if you
21 give me a second, I can find his exact statement.

22 "These results indicate that the zymogen
23 Factor C is isolated from hemocytes of American and
24 Japanese horseshoe crabs respectively are identical
25 protein entities both immunologically and

1 biochemically."

2 So they considered them so equivalent that,
3 for the remainder of their study, they focused on the
4 Tachypleus Factor C, because they expected identical
5 results from the two enzymes based on what they already
6 knew.

7 So I think a POSA would consider the data
8 from this study in total, and they would agree with
9 Dr. Tokunaga that there's no appreciable difference in
10 biochemical behavior between the enzymes from the two
11 species; and, thus, you would expect any of these
12 biochemical events that are required for activity,
13 including these protease cleavages, to behave in a very
14 similar manner, certainly a functionally equivalent
15 manner, even with the identified differences in
16 sequence.

17 Q. But we acknowledged at the beginning of
18 this questioning that Tokunaga was not studying a
19 reporting on residual activity; right?

20 A. Well, I also think for the last 10 minutes
21 or so, we haven't discussed residual activity at all.
22 Yes, we agreed that Tokunaga was not discussing residual
23 activity because he was not in the business at this
24 point of purifying Factor C and testing Factor C under
25 the conditions -- under the many possible conditions

1 under which it might have been used in a Factor C assay.

2 That is not the point of this study.

3 The point of this study is a more basic
4 biochemical characterization, primarily of the
5 Tachypleus Factor C, but with enough study of Limulus
6 Factor C that they conclude that everything that they
7 found for the Tachypleus Factor C would apply to the
8 Limulus Factor C as well.

9 Q. Do you know if the reported error that you
10 note in Supplemental Figure 7S regarding that
11 carbohydrate attachment site was corrected by Tokunaga
12 or anyone associated with this paper subsequent, before
13 the sequence -- Limulus polyphemus sequence actually was
14 published?

15 A. I did not investigate that possibility, so
16 I can't say one way or the other.

17 Q. Okay. Now, Tokunaga also reports on the
18 enzymatic activity of Limulus polyphemus and Tachypleus
19 Factor C; right?

20 A. Can you point to a specific figure?

21 Q. Yeah. So I'll point you just to -- I think
22 they took a look at chymotrypsin-mediated activation of
23 Factor C in Figure 2?

24 A. Uh-huh.

25 Q. You agree that the reported activity is

1 between Factor C from Limulus versus Tachypleus are
2 different; right?

3 A. You're going to have to give me a minute to
4 remind myself of exactly what's in this figure.

5 Q. Okay.

6 A. So for a number of reasons, it's actually
7 very hard to compare panel A, which is the Tachypleus
8 Factor C, with panel B, which is the Limulus Factor C.
9 This includes the fact that if you look at -- if you
10 compare the amount of enzyme used for Limulus in the
11 legend, 95.6 micrograms per mL, that's the concentration
12 there, it does not say in the legend how 110 Tachypleus
13 Factor C was used. But you have to go back to materials
14 and methods.

15 Q. Uh-huh.

16 A. And there, it says that the, presumably,
17 Tachypleus Factor C was used at 206 micrograms per mL.

18 Q. Uh-huh.

19 A. So pretty different concentration.

20 And then looking at the X axis, the
21 incubation time, those are distinct. So we have a full
22 150 minutes for the Tachypleus; we have only six minutes
23 for the Limulus; and then the Y axis is also on a
24 somewhat different scale. It's a little easier to try
25 to compare between those.

1 But at any rate, there are some key
2 differences in the experimental design, specifically the
3 concentration of the two factors. We don't even know
4 that they were purified in the same way, how pure they
5 were, so it's very hard to compare them.

6 Q. Okay. So are you saying a person with
7 skill in the art looking at this data in Tokunaga would
8 not be able to draw a conclusion about similarity or
9 difference of enzymatic activity?

10 MS. LO: Objection to form.

11 A. Well, again, I think you are asking the
12 question from a perspective of whether the assay is
13 reading out identical numerical data; and a POSA looking
14 at this experiment wouldn't even be looking through that
15 lens.

16 One, they were clearly not performed at the
17 same time because they're not even shown in the same
18 graph.

19 So what a POSA would be more likely to
20 absorb from this and focus on is the fact that alpha
21 chymotrypsin activates both enzymes relatively
22 efficiently by the shape of the curve and given how
23 quickly this is happening.

24 So, you know, nobody is going to be
25 comparing the numerical values here for the reasons that

1 I've already outlined. It's more of the fact that both
2 of these are responsive to this same protease.

3 BY MS. LOUGHRAN:

4 Q. Just turning back to the 7S and 8S below
5 it, in 8S, there's a little diagram of Limulus
6 polyphemus Factor C. And there's an X sort of
7 superscript serine, and I guess an X subscript
8 isoleucine; do you see that?

9 A. I do see that.

10 Q. What is the significance of those Xes?

11 A. The significance of the Xes were that those
12 amino acids were not yet known. So what's shown above
13 in 7S is the admin degradation sequencing whether
14 they're determining N-termini. So based on the
15 N-terminal sequences for what's called both A and L, the
16 N-terminus we know is the serine. So the serine was
17 there.

18 But we don't have C-terminal sequence for
19 the heavy chain so we're calling that X because we don't
20 know definitively what that amino acid is.

21 And similarly for the N-terminus of B, we
22 know that the first residue there is isoleucine. And so
23 the isoleucine is indicated.

24 But on the other side, which is the
25 C-terminus of A, we don't yet know that amino acid,

1 because we didn't have sequencing from the C-terminus or
2 enough sequencing from the N-terminus to identify that
3 specific amino acid.

4 Q. All right. I'm going to hand you a
5 different document. And I think it's a document that
6 you've referenced in your declaration that's been marked
7 as Exhibit 2035.

8 (Exhibit 2035 was introduced to the
9 witness.)

10 BY MS. LOUGHRAN:

11 Q. And this is Exhibit 2035 in the IPR. It's
12 also cited in the PGR declaration. It's a publication
13 to Inventor Chen.

14 Do you recognize this one?

15 A. I believe I do.

16 Q. Okay.

17 A. Yes.

18 Q. Now, I think you cite to this, because the
19 inventors here reported on the results of some tryptic
20 mapping. So now we're going back to the concept of
21 tryptic mapping; is that right?

22 A. You'll have to point me to where it's
23 discussed in the declaration.

24 Q. Sure. So if you'll look at paragraph 34,
25 for example -- yeah.

1 A. Yes.

2 Q. Okay. So you cite here this exhibit, which
3 is 2035, as evidence of tryptic peptide sequencing
4 revealing, et cetera, et cetera.

5 Do you see that?

6 A. Yes.

7 Q. Okay. Now, it is true that -- well, strike
8 that.

9 What is tryptic mapping, tryptic peptide
10 sequencing?

11 A. As I described before, you will take your
12 target protein, the one that you want sequence
13 information on. You will incubate it with trypsin.
14 Trypsin will cut it at specific sites. You know, like
15 all proteases, trypsin is a site-specific protease.
16 It's fairly promiscuous. But it will cut in specific
17 sites that will give you a series of free N-termini. So
18 now you don't have an intact protein anymore, you have a
19 functional peptide of varying length, depending on where
20 the trypsin sites are.

21 And then you would do the same kind of
22 sequencing that Tokunaga did, the admin degradation. So
23 all of the free N-termini can then be sequenced for a
24 certain length.

25 Q. And so in this publication, the inventors

1 report that tryptic peptide sequencing revealed greater
2 than 90 percent sequence identity; do you see that?

3 A. I do see that.

4 Q. Okay. The tryptic sequencing, that doesn't
5 give you a full cDNA or amino acid sequence for the
6 entire protein; right?

7 A. Correct. That will give you, you know, the
8 same kind of information that Tokunaga had, except it
9 will give you more because now you've cleaved with
10 trypsin. So now, in addition to the end of the heavy
11 chain, the end of the light chain, the end of the A
12 chain, you will have a number of free N-termini. So you
13 get much more.

14 It's indicated in the way they indicate the
15 level of identify as well, as greater than 90 percent.
16 They don't give you a highly specific number. They're
17 giving you, you know, a -- close to this number.

18 Q. But so it's greater than 90 percent of some
19 percentage that --

20 A. Correct.

21 Q. -- Trypotan is able to identify?

22 A. Correct. I would point out that we haven't
23 covered the rest of that paragraph yet, where there are
24 a couple of other references where they call out much
25 more exact numbers.

1 So further down in the paragraph, I'll just
2 read the section now. Other publications disclosed
3 similar information in 2006 and 2009. Exhibit 2036 at
4 4, the Factor C of Carinoscorpius rotundicauda has
5 89.3 percent homology, with that of Limulus polyphemus.

6 Exhibit 2049 at 2, the recombinant Factor C
7 protein derived from Carinoscorpius rotundicauda shares
8 90.5 percent identical amino acid sequence with a native
9 Factor C protein derived from Limulus polyphemus.

10 So in those two publications, they're
11 calling out much more specific numbers suggesting that
12 they had probably sequenced all or nearly all of the
13 protein, if they're going to give a number that is that
14 precise.

15 Q. Yeah. But the number that they gave
16 between those two publications actually was different;
17 right?

18 A. There is some disagreement there.

19 Q. Okay.

20 A. That's how science goes sometimes. Not
21 everybody comes up with the same answer.

22 Q. Now, again, this Chen publication doesn't
23 say -- it doesn't measure residual activity of these
24 proteins; right?

25 A. I do not recall that being part of Chen,

1 although they do a number of other kinds of studies. I
2 think this one was mostly focused on detergents.

3 A. Yes. Great.

4 Q. So these inventors report on some studies
5 about how recombinant Carcinoscorpis --
6 Carcinoscorpis -- sorry -- recombinant Carcinoscorpis
7 Factor C is enhanced or inhibited by zwittergent
8 detergent; right?

9 A. Uh-huh.

10 Q. Okay. You just have to say yes.

11 A. Oh, sorry. Yes.

12 Q. And then they compare that to how native
13 Limulus polyphemus Factor C is enhanced or inhibited by
14 the same detergent; right?

15 A. I believe they do that comparison in, yes,
16 the -- one of the important parameters here is that they
17 are comparing a recombinant to a purified.

18 Q. And as we saw from the inventor's own work,
19 Figure 7 that we were looking at different -- Figure 7
20 that we were looking at earlier, you would expect
21 recombinant and native to have different activities;
22 right?

23 A. Well, I would not necessarily make that
24 leap of faith. We know at least as far as residual
25 activities in the presence of the various inhibitors

1 that were discussed in both '318 and '109, that there
2 were differences seen in those assays. I would not
3 necessarily want to extrapolate those data to behavior
4 in detergents.

5 It's -- I guess I would say a POSA would
6 have a reasonable expectation that the behaviors might
7 be different, but I don't know that a POSA would make
8 any predictions beyond that, again, because it's not an
9 apples-to-apples comparison. In one case, we're talking
10 about ionic composition; in this case, we're talking
11 about detergents.

12 Q. Okay. But have you looked at the results?
13 You're looking at them.

14 So Figure 1, for example, is -- shows the
15 recombinant Factor C activity ratio. The black bars are
16 for the detergent; right?

17 A. I believe we have two different detergents
18 here. I think ZW is a zwittergent detergent and Tween
19 20 I think is thick detergent.

20 Q. Yes. And then Figure 6 is the results for
21 Limulus in the zwittergent detergent; right?

22 A. That is how Figure 6 is labeled, yes.

23 Q. Okay. And so in Figure 1, peak -- I guess
24 enhancement for recombinant Factor C occurs around
25 .001 percent?

1 A. Looking at that data, that appears to be a
2 reasonable summation of what is shown, yes.

3 Q. Okay. And then for Limulus, it appears
4 that peak enhancement is -- occurs around .005 percent;
5 do you see that?

6 MS. LO: I'd like to interpose an objection
7 to this line of questioning about the results as outside
8 the scope.

9 A. I do see that. I would add to my response,
10 though, that I do not -- since, you know, these are two
11 completely different figures, I have no confidence that
12 these two experiments were performed in a comparable
13 manner.

14 I would also note that the range of
15 detergent concentrations is completely different in
16 these two experiments. So, for example, in Figure 6, it
17 does not even appear that a .001 concentration was
18 actually tested. So it's exceedingly difficult to try
19 to compare data between these two experiments.

20 BY MS. LOUGHRAN:

21 Q. Okay. Would you agree that a POSA would
22 not be able to make any predictions about residual
23 activity between species based on the experiments
24 described here?

25 MS. LO: Objection, outside the scope.

1 A. Yeah. From my understanding, in the case
2 of these proceedings, when we're discussing residual
3 activity, we're discussing residual activity
4 specifically as it pertains to the activity of Factor C
5 in very specific salt solutions.

6 In these figures that you're having me look
7 at, there's no -- there's no reported difference,
8 anyway, between the salt content in these various
9 experiments. It's all detergent.

10 And detergent and the salt ions in question
11 are completely different entities. So I don't see where
12 one would take these data and make a specific conclusion
13 about residual activity.

14 BY MS. LOUGHRAN:

15 Q. Okay. Now, you also cited, I think in that
16 same paragraph that we were looking at, Exhibit 2036,
17 which you cited in both the IPR and the PGR. And this
18 is an article by Alwis about some house dust study; do
19 you see that?

20 A. I do see that.

21 Q. Do you recognize this document as one you
22 cited?

23 A. I do.

24 Q. Okay. Now, this was, again, a comparison
25 between the LAL Factor C, Limulus polyphemus Factor C

1 and recombinant Carcinoscorpius protein; right?

2 A. Yes.

3 Q. All right. And you cite this because it
4 says the Carcinoscorpius has 89.3 percent homology with
5 that of Limulus polyphemus; do you see that?

6 A. Yes.

7 Q. Okay. Now, that cites Lin Chen personal
8 communications; do you see that?

9 A. Yes.

10 Q. So nobody, again, has provided a sequence
11 for Limulus polyphemus from which anyone could verify
12 those numbers; right?

13 MS. LO: Objection to form.

14 A. I do not really know how to answer that
15 question, other than to say I am not aware of a
16 publication from the person from whom that information
17 came, and Dr. Chen, who is cited there as the source of
18 the personal communication.

19 In this case, we can assume that that
20 number was derived by an investigator working in this
21 field who did not divulge it in a public communications,
22 but was willing to communicate that overall result to
23 the authors of this paper.

24 BY MS. LOUGHRAN:

25 Q. What allows you to assume that, Doctor?

1 A. What am I assuming?

2 Q. Well, you said, "We can assume that the
3 number was derived by an investigator working in this
4 field."

5 A. Yes.

6 Q. Why can you assume that?

7 A. I guess I would answer that by saying it is
8 highly unlikely that a person not working in the field
9 of horseshoe crabs or Factor C or things related to
10 Factor C would have bothered to derive the sequence of
11 this enzyme.

12 Q. Okay. Well, Lin Chen was the inventor on
13 the publication that we just looked at; right?

14 A. Uh-huh.

15 Q. Who reported greater than 90 percent
16 homology; right?

17 A. Okay.

18 Q. Is that correct?

19 A. Well, I think -- I don't know that we had
20 an identification of the person that was that specific.
21 I think you said -- can you point me to where it is?

22 Q. Yeah. If you look back at the publication
23 that we were just looking at, the detergent one, the
24 first page.

25 A. Yeah. I'd like to look at this one where

1 the name of the author is called out, the name of the
2 personal communication.

3 Q. Yeah. So it's page 4 of 5 in the top of
4 the right-hand column.

5 A. Okay. Lin Chen communication. Yes. Okay.

6 Q. So those two reports from Lin Chen are
7 different; right?

8 A. The numbers are different. And -- okay.
9 Publication date 2003, publication date 2006. So
10 although I do not have any concrete means of assessing
11 this, I would say the POSA would reasonably conclude
12 that between the time of this patent application in 2003
13 and this publication in 2006 that cites a personal
14 communication with Lin Chen, that Dr. Chen had gone on
15 from the tryptic peptide sequence data to perform some
16 PCR with those sequences, using primers derived from
17 those sequences to obtain the full sequence of Factor C.

18 Clearly, Dr. Chen is interested in using
19 these proteins and assays and it would, thus, be
20 advantageous to have the sequence of the entire protein.

21 Q. But Dr. Chen didn't publish it; right?

22 A. There may have -- Dr. Chen does not seem to
23 have published it. I have not come across anything like
24 that. There could both have been no incentive to
25 publish it and perhaps a disincentive to publish it if

1 they had intended to, at some point, for example,
2 disclose it later in a patent application after a patent
3 had been secured.

4 Q. Now, the author of this publication in the
5 paragraph -- the top of the paragraph that we were just
6 looking at -- so just before I get there, do you -- is
7 it your position or do you believe that this
8 89.3 percent reported homology is more accurate than the
9 greater-than-90-percent homology that was reported for
10 the tryptic mapping?

11 A. Just on its face, it is a more precise way
12 of reporting the data. Greater than 90 percent simply
13 establishes a threshold. The homology is believed by
14 the person who did the assay to be at greater than
15 90 percent; whereas saying 89.3 suggests that the person
16 who communicated that number had done an analysis to the
17 point that that was the value that they believed to be
18 accurate.

19 Q. Now, the report on this publication, "This
20 comparison between LAL and rFC, under the discussion,
21 the authors say the LAL estimates were higher compared
22 with rFC estimates for all the samples we assayed. And
23 larger differences between LAL and rFC were
24 significantly correlated with larger LAL estimates of
25 endotoxin content."

1 Do you see that?

2 A. Uh-huh.

3 Q. It's at sort of the beginning of the
4 paragraph we were just looking at on page 4.

5 A. On page 4? Which paragraph, again? Sorry.

6 Q. Yeah. So the second paragraph of the
7 discussion. It says LAL estimates are higher.

8 A. Yes. Okay. I do see that.

9 Q. And the authors attribute that to the
10 species differences between those two proteins; do you
11 see that?

12 MS. LO: Objection to form.

13 A. I do see that sentence.

14 BY MS. LOUGHRAN:

15 Q. Okay. And then they talk about the
16 homology, which you have quoted in your declaration.

17 A. Uh-huh.

18 Q. And at the very end of that paragraph, they
19 say, "Subtle differences in the responsiveness of Factor
20 C from these species may account for their small, but
21 systematically different results."

22 Do you see that?

23 A. I do see that.

24 Q. So at least with respect to the results
25 here --

1 A. Okay. Finish. I'm sorry.

2 Q. -- there is some attribution of differing
3 results to differing species; right?

4 A. So I want to clarify that what we just read
5 is not in the Results section of the paper, it's in the
6 Discussion section of the paper. Discussion sections
7 are inherently more speculative in their conclusions.
8 So I am hesitant to draw any conclusions from what is
9 written here simply because of where it appears in the
10 paper.

11 This is the author's interpretation of
12 their data in comparison to, you know, various other
13 facts, including this personal communication, and
14 other -- other references that they're citing. Anything
15 in the discussion is going to be more speculative in
16 nature. So I would not call these conclusions. I would
17 call this inherently speculation, because it appears in
18 the Discussion section.

19 Q. Does a POSA read the Discussion section of
20 peer-reviewed articles?

21 A. Not necessarily.

22 MS. LO: Objection to form.

23 A. A POSA is going to pay the most attention
24 to the Results section, and actually, to the data
25 themselves. Whether a POSA reads the discussion or not

1 is really a matter of personal choice. You know, again,
2 Discussion sections tend to reflect the views and even
3 the biases of the person or persons writing the paper.

4 So if a POSA really wants to know what a
5 particular scientific publication says, they're going to
6 focus first on the actual data, and then on the Results
7 section, which is a bit more cut and dry and is at least
8 supposed to be relatively free of bias, opinion and
9 speculation.

10 BY MS. LOUGHRAN:

11 Q. Okay. Well, in your declaration, you cite
12 Tokunaga's description of Tachypleus and Carcinoscorpius
13 being indistinguishable in terms of immunological and
14 biochemical properties; right?

15 A. I do.

16 Q. And you know that appears in the discussion
17 section of Tokunaga?

18 A. I believe it appears in the Results section
19 of Tokunaga.

20 Q. If you look at the Discussion section on
21 page 153 --

22 A. Hold on just a second. Okay. I am reading
23 on page 152, clearly, the Results section. "These
24 results indicate that the zymogen Factor C is isolated
25 from hemocytes of American and Japanese source of crabs,

1 respectively are identical protein entities both
2 immunologically and biochemical results."

3 They may repeat that in the discussion, but
4 it's immaterial.

5 Q. Okay. But you do recognize if you look at
6 the Discussion section there --

7 A. Again, essentially, the same sentence is
8 repeated in both Results and Discussion. Results takes
9 precedence because it's in a section that is relatively
10 free from bias. It's in both sections. Sometimes --
11 many times authors repeat what they report in Results in
12 Discussion as part of their narrative.

13 Q. Okay. You agree that in the Results
14 section of the Alwis publication, which is Exhibit 2036
15 that we were looking at, if you look at the second
16 paragraph, on page 3 of 5 under Results --

17 A. Yes.

18 Q. -- "LAL consistently produced higher
19 endotoxin estimates compared with rFC."

20 Do you see that?

21 A. I see that.

22 Q. So a POSA could read that under your
23 standard of what you could take out of a publication and
24 would say -- would look at that as a result and
25 understand that Limulus polyphemus native Factor C gave

1 different higher endotoxin estimates compared with
2 recombinant Factor C for a different species; do you
3 agree with that?

4 A. That is actually not what the authors have
5 stated in the results. That sentence simply says, "LAL
6 constantly produced -- consistently produced higher
7 endotoxin estimates compared with recombinant Factor C."

8 So species is not called out there.
9 Perhaps you can find somewhere where it is. But in that
10 particular sentence, reporting the results, the species
11 is not called out.

12 Q. Well, species is not called out. But LAL
13 is *Limulus polyphemus* Factor C; right?

14 A. Yes, we can agree to that.

15 Q. And rFC there is *Carcinoscorpius*
16 recombinant Factor C; right?

17 A. In this particular study, it was. But in
18 this particular section, they're not drawing any
19 attention to the species of either the purified or the
20 recombinant.

21 Q. Okay. Fair that they're not drawing any
22 attention to the difference in species, but you do agree
23 that those two Factor C proteins came from different
24 species; right?

25 A. They came from different species. One was

1 purified, one was recombinant, and, you know, without
2 looking very carefully at the methods, we really know
3 nothing about how either one of these was produced.

4 So my point in bringing that up is there's
5 a universe of possibilities for why they got different
6 results from purified protein versus the recombinant
7 protein, you know. It is entirely possible that the way
8 that they were preparing the recombinant protein was an
9 inferior biochemical technique that somehow damaged the
10 protein.

11 Later, in the Discussion section, they
12 speculate about possible reasons why and they relate it
13 to the species. I have no idea why they called out the
14 species, because, again, there's a universe of possible
15 reasons why they might have gotten different results
16 from the native prep; that is, the prep that was
17 harvested and purified from crabs, versus the
18 recombinant prep that was produced with some sort of
19 recombinant methodology, which I don't remember off the
20 top of my head.

21 But them speculating about it being a
22 species-based difference is simply that. It's
23 speculation. And I don't really see any basis to
24 conclude that with any degree of certainty.

25 Q. Okay. When you say there's a universe of

1 reasons why they may have gotten different results,
2 would a POSA, in 2013, have understood that?

3 A. Yes. I think a POSA in 2013 would have
4 understood that. It's not an apples-to-apples
5 comparison. They are comparing a purified protein to
6 recombinant protein. And those two proteins were
7 prepared in completely different ways, probably most of
8 which is unknown, based on what is in that paper.

9 So the -- you know, the preparation can --
10 and many different aspects of the preparation can have a
11 tremendous impact on what comes out the other end.

12 So, you know, based on the data that are
13 shown here, which are very limited, I don't see any
14 reason to ascribe the differences in activity to
15 anything in particular. They found that there were some
16 differences in activity.

17 The point of this study was to rule out the
18 idea that it might be these beta glucans detected by
19 Factor G in the native prep that, you know, that give a
20 contaminating activity. Factor G also activates the
21 terminal protein in the clotting cascade.

22 And so if there are these beta glucans
23 which are produced naturally by fungi, these beta
24 glucans contaminate a lot of things. They can give a
25 false positive or a false amount of signal. And with

1 the purified LAL reagent, that is not seen with the
2 recombinant assay because Factor G is not there.

3 The whole point of this paper was to say,
4 hey, the differences we see are real and they're
5 actually not due to Factor G. One study. But that's
6 what they concluded.

7 (Exhibit 2049 was introduced to the
8 witness.)

9 BY MS. LOUGHRAN:

10 Q. Okay. And in paragraph 34 of your
11 declaration, you also cite Exhibit 2049. Do you
12 recognize this document?

13 A. I do.

14 Q. And this is also cited in your declaration
15 on the point about homology, although here at page 2 of
16 9, the reported homology is 90.5 percent; do you see
17 that?

18 A. I do see that.

19 Q. Okay. So now we're back to over
20 90 percent; correct?

21 A. Correct.

22 Q. Still not based on any published sequence;
23 right?

24 A. Not based on any published sequence as far
25 as I know. And I'll take this opportunity to point out

1 that the difference between 89.3 percent and
2 90.5 percent is not huge.

3 Q. Okay.

4 A. They came to very similar results, similar
5 conclusions.

6 Q. Well, this publication was now published in
7 2009; right?

8 A. Yes.

9 Q. So we had, in 2003, a report of greater
10 than 90 percent, that in 2006 a report of 89.3 percent,
11 which you indicated would have been based on a more
12 precise methodology. And now in 2009, the reported
13 homology is 90.5 percent; right?

14 MS. LO: Objection to form.

15 A. You have recited the same numbers that are
16 present in my paragraph 34. I will stand by the text
17 that is written in paragraph 34.

18 BY MS. LOUGHRAN:

19 Q. Now, Dr. Schaefer, just to finish the
20 thought that we were discussing before, you had
21 indicated that there's a universe of reasons why, you
22 know, in the Alwis publication, the researchers got
23 different results; right? We talked about that.

24 A. There's a universe of reasons that they
25 could have gotten different results. And I did not see

1 anything in their data that would point to a difference
2 between species simply because what they were comparing
3 was not prepared in the same manner.

4 We have a purified enzyme versus a
5 recombinant enzyme. And to me, it seems exceedingly
6 speculative that they decided to introduce the idea that
7 it might be a species difference, rather than anything
8 else that there might have been, given that those two
9 proteins were prepared in such a different manner.

10 Q. Okay. And so the difference in results
11 would not be attributable to the particular homology
12 reported there; right?

13 MS. LO: Objection to form.

14 A. That's not really the correct way to use
15 the word homology. We can say similarity. Homology is
16 binary --

17 BY MS. LOUGHRAN:

18 Q. Okay.

19 A. -- whether two things are homologous or
20 they're not. Similarity, we're talking about
21 quantitative measures, which I believe is what we're
22 talking about here.

23 Q. Fair enough. So they reported on some
24 level of similarity between these species, unpublished
25 data, but something that they understood?

1 A. Yes. They reported 90.5 percent identical
2 amino acid sequence.

3 Q. Okay. But that does not allow a prediction
4 about how the proteins will actually -- let me strike
5 that.

6 That 90.5 similarity does not enable a
7 prediction of the specific activity of those proteins in
8 these assays; right?

9 MS. LO: Objection to form.

10 A. Any specific piece of data by itself is
11 rarely able -- rarely enables you to make impactful
12 conclusions. But that is not the only piece of data
13 that a POSA has, far from it. So much more important,
14 even, than this particular number that they give for
15 identical amino acids between the two species -- and,
16 again, we're not talking similarity here, we're talking
17 identity -- is the fact that these enzymes were both
18 very well characterized in purified form from the crabs
19 themselves.

20 And in that extensive biochemical
21 characterization where now we're comparing apples to
22 apples, you have a purified protein from Limulus, we
23 have a purified protein from Tachyplesus or a purified
24 protein from Carinoscorpius. And we know they behave
25 in a functionally interchangeable manner.

1 You know, the 90.5 percent identical amino
2 acid sequence is sort of icing on the cake. It tells
3 you, wow, these are really, really closely related, in
4 addition to being functionally indistinguishable, they
5 are genetically very, very close.

6 BY MS. LOUGHRAN:

7 Q. When you say the apples to apples, we have
8 purified Limulus and purified Tachypleus or purified
9 Carcinoscorpius. And we know they behave in a
10 functionally interchangeable manner.

11 What are you referring to there? What is
12 the apples-to-apples comparison you're referring to
13 there?

14 MS. LO: Objection to form.

15 A. Apples to apples, now we're talking about
16 purified protein versus purified protein. Before when
17 we were discussing Alwis, in their study, it was apples
18 to oranges. It was purified protein compared to
19 recombinant protein.

20 So those two proteins were not prepared in
21 a similar manner, and they're drawing conclusions that
22 are -- where they're extrapolating a great deal to say,
23 you know, we see differences that are dependent on the
24 fact that these are from a different species when the
25 entire preparation of those enzymes was very, very

1 different.

2 BY MS. LOUGHRAN:

3 Q. Right. I'm just asking when you -- are you
4 pointing to a particular paper that has that
5 apples-to-apples comparison, the native to native?

6 A. I don't know that I'm pointing to a -- no,
7 I'm not pointing to a specific paper. We are just
8 talking in general about what was known. So what was
9 known from studies of purified proteins, okay, I can
10 point to a specific paper.

11 In Tokunaga, they were comparing purified
12 protein to purified protein. When we're looking at the
13 pharmacopeias, when they were -- I'm losing the word.
14 When they were harmonizing the pharmacopeias for the
15 assays from the purified proteins, they were comparing
16 purified protein to purified protein.

17 Okay. So in those cases, both in the early
18 biochemical studies and in the studies of the assay
19 reagents, where the assay reagents being compared were
20 the purified proteins, those were side by side, purified
21 proteins in the same or highly similar manners.

22 Q. I'm sorry. I thought that when we looked
23 at Tokunaga, we looked at the kinetic data, chymotrypsin
24 reports for Tachypleus and Limulus. You said they
25 couldn't be compared?

1 A. In that particular figure, you were asking
2 me to make numerical comparisons. And I said you cannot
3 take those two figures and make an exact numerical
4 comparison. That's not the comparison that Tokunaga was
5 making. The comparison that Tokunaga was making was,
6 hey, look, both of these enzymes are activated by
7 chymotrypsin and not by trypsin.

8 So it was a more qualitative, mechanistic
9 examination. They were not concerned with the numbers.
10 They were concerned with showing the activities were the
11 same.

12 Q. Okay. Understood.

13 MS. LO: Can we take a break?

14 (A break was taken.)

15 BY MS. LOUGHRAN:

16 Q. Hello again, Dr. Schaefer. How are you?

17 A. I'm good.

18 Q. If you could just look at paragraph 101 of
19 your declaration.

20 And you say, "Researchers had also
21 established comparable function between commercially
22 available recombinant Carcinoscorpius rotundicauda
23 Factor C and the native lysate-based endotoxin assays by
24 December of 2013."

25 Do you see that?

1 A. I see that.

2 Q. Now, I think based on the discussion we
3 were having at the break, when you say comparable
4 function, you're talking about -- so, for example, if
5 you look at the exhibit that you just -- you have in
6 front of you right now, like the cascade that appears on
7 page 2; is that right?

8 A. Both reagents were considered perfectly
9 appropriate for performing LAL assays for the testing
10 for endotoxin.

11 Q. Okay. And so if you look at -- and, again,
12 this is where, you know, the authors talk about this
13 90.5 percent identical amino acid sequence. The actual
14 comparisons they did here -- so, for example, if you
15 look at Figure 3, which is on page 4 --

16 A. Yes.

17 Q. -- so they did show differences in
18 activity; right?

19 A. There are some differences shown, depending
20 on what the specific source of LPS is.

21 Q. Okay. So, for example, I believe like the
22 chromogenic and the turbidometric sources are LAL-based;
23 right?

24 A. That would be my understanding, yes.

25 Q. Okay. And then the rFC is the

1 recombinantly produced protein; right?

2 A. Yes.

3 Q. So when you look, for example, in Figure 3,
4 the lanes for pseudomonas and salmonella, the LAL-based
5 turbidometric assays had higher endotoxin potency than
6 the recombinant-based; is that fair?

7 A. That is what the table shows, or what the
8 figure shows.

9 Q. Okay. So even though the two
10 methodologies, the LAL-based, which is Limulus
11 polyphemus, and the recombinant, which is
12 Carcinoscorpius, have different specific activities as
13 shown in Figure 3, it's your opinion that they're
14 comparable in terms of function; is that -- am I
15 understanding you correctly?

16 A. I'm sorry. Can you repeat the question?

17 Q. Sure. So even though the two
18 methodologies, one LAL-based, which is Limulus
19 polyphemus Factor C and recombinant, which is
20 Carcinoscorpius Factor C, has have different specific
21 activities as shown in Exhibit 3, it's your testimony
22 they're comparable in terms of function; is that a fair
23 assessment?

24 MS. LO: Objection to form.

25 A. I would answer by saying that based on the

1 very, very, very limited data that they show on -- you
2 can include that both reagents successfully detect
3 endotoxin.

4 And then based on, you know, everything we
5 know about these assays across species, we know that
6 both the recombinant-based assay and the
7 purified-enzyme-based assay, both assays detect
8 endotoxin with similar sensitivity.

9 BY MS. LOUGHRAN:

10 Q. Okay. But you recognize, for example, that
11 the -- so, I mean, if you look at the summary of this on
12 page 5, the first paragraph, it says, "The two LAL-based
13 procedures gave statistically significant different mean
14 responses for all four endotoxin sources."

15 Do you see that?

16 A. I do see that.

17 Q. Okay. So it's more than just, oh, they
18 successfully detected endotoxin; right?

19 A. Yes.

20 Q. Quantitatively, the LAL procedures had
21 higher endotoxin potency metrics; right?

22 MS. LO: Objection to form.

23 A. In the specific assay that they ran in
24 Figure 3, with seemingly a single unnamed concentration
25 that was tested, they got distinct results.

1 They got distinct results, although the
2 results were not impressively different between the
3 first two sources, really; it's just the second two
4 sources, the pseudomonas and the salmonella. And only
5 when the turbidometric assay was used and not the
6 chromogenic assay. So I'm hesitant to draw global
7 solutions about LAL versus the recombinant based on
8 that.

9 BY MS. LOUGHRAN:

10 Q. I'm not asking you to draw global solutions
11 or conclusions. I'm just saying you are concluding that
12 these are functionally, what do you say, comparable;
13 right?

14 A. Functionally comparable. That doesn't mean
15 you can't come up with an assay and assay conditions
16 here and there where you get a numerical output that is
17 somewhat different. But, again, we know from the
18 pharmacopeias that both the recombinant assay and the
19 assay -- the purified enzymes are accepted, and not only
20 are they accepted, they're understood to give you
21 comparable, real-world working values.

22 You know, if you test an antibody solution
23 that's going into a patient with the recombinant assay
24 and you test that same reagent with the purified enzyme
25 assay, you're going to get the same result, endotoxin

1 versus no endotoxin.

2 Q. Okay. And just to be clear, when you say
3 you're going to get the same result, endotoxin versus no
4 endotoxin, that is after you have standardized based on
5 the calibration, the international calibration
6 requirement; right?

7 A. That is after using the assay in the way
8 that it's directed to be used. Whatever that entails,
9 following all the directions very precisely in a manner
10 that is consistent with what is in directions for the
11 assay and spelled out by -- you know, in this case,
12 regarding testing for a medical device and a medical
13 solution, by the relevant pharmacopeias.

14 Q. You also cite Exhibit 2075 in paragraph
15 101. This is Exhibit 2075, Forn, et al.

16 (Exhibit 2075 was introduced to the
17 witness.)

18 BY MS. LOUGHRAN:

19 Q. Now, this, again, I think was a comparison
20 between LAL and recombinant Carcinoscorpius Factor C;
21 right?

22 A. That is correct, yes.

23 Q. Okay. I think the researchers took
24 samples, samples in labs and then sort of in the field
25 at like dairy farms and things like that. Is that what

1 you recall about this study?

2 A. That's my recollection, yes.

3 Q. Okay. And so if you look at -- there's a
4 graph on page 5 of Figure 5. And it has proportional
5 differences in endotoxin detection assays by facility.

6 Do you see that graph?

7 A. I do.

8 Q. Okay. And it sort of shows sometimes the
9 recombinant Factor C gave a higher value than sometimes
10 LAL, and it sort of depends. It goes up and down
11 depending on particular facilities; do you see that?

12 A. I do see that.

13 Q. Okay. So, again, your view is that the
14 data in this publication shows that the two assays are
15 comparable, even though, in any given comparison between
16 those two proteins, you may get different results;
17 right?

18 A. Well, I would point out that the
19 proportional differences shown are pretty slight. You
20 know, the highest appears to be .2, which, to me,
21 equates to a 20 percent difference.

22 The other thing I would point out is that
23 there are no error bars whatsoever on any of those dots.
24 So it is very difficult to know what the range of data
25 were. And it's very hard to evaluate that figure as far

1 as how much we really trust those data. Is it simply
2 noise, or are those real differences?

3 But even if they are real differences, the
4 amount of difference seems not particularly meaningful.

5 Q. Okay. But I didn't -- you cited this
6 publication in your declaration to make a -- to draw a
7 particular conclusion. So I'm just trying to understand
8 from where in this publication you're drawing that
9 conclusion.

10 A. Again, you would come back to the
11 proportional difference. It's small. And the main
12 thing that I take home from looking at all of these data
13 is that, you know, really, the mean is at zero, and most
14 of the dots follow very close to zero. So in the great
15 majority of cases, they're comparable.

16 Q. But you agree that, in some instances, you
17 will see differences; right?

18 A. In some instances, you may see differences.
19 But that -- you know, from a functional capacity, a POSA
20 would understand that these differences are not
21 considered meaningful in the majority of real-world uses
22 of this assay.

23 I say the majority because maybe there are
24 exceptions that I'm unaware of. But at least as far as
25 what the various pharmacopeias regulate, they say that

1 the assays are equivalent, period.

2 Q. Well, you're saying that the differences
3 are not considered meaningful. But they were meaningful
4 enough to be published in this paper that you've cited;
5 right?

6 MS. LO: Objection to form.

7 A. Give me a minute to review the conclusions
8 of the authors. Yeah. No, I don't agree with that
9 statement. The penultimate sentence in the abstract is,
10 "The data from this study demonstrate the LAL assay, and
11 the recombinant Factor C assay return similar estimates
12 of exposure in livestock facilities."

13 That, to me, is a conclusion that says they
14 are extremely similar; you can use either one.

15 BY MS. LOUGHRAN:

16 Q. Well, okay. That's their conclusion;
17 right? They're saying that they're similar?

18 A. Yes.

19 Q. But the data points that they are giving do
20 show that there are differences; right? Maybe we're
21 drawing a distinction between like -- similar allows for
22 there being actual measurements that are different;
23 right?

24 MS. LO: Objection to form.

25 A. In a scientific paper, if you ever see data

1 points where you run a series of comparisons, and they
2 all come out with exactly the same number, you can be
3 pretty sure that the person is committing some sort of
4 scientific fraud. It's just -- it's not how things
5 work. There's always going to be some level of
6 difference.

7 You know, if you take the microscope and
8 look at something at high enough power, you're
9 eventually going to find a difference. You know, maybe
10 it's not until you get to the atomic level.

11 So no two things, you know, we're talking
12 about humans, identical twins, if we're talking about
13 product, no two products, if you look at them close
14 enough, they're never identical.

15 So the idea that there is going to be a
16 perfect correlation in every run in every instance in
17 these two assays is -- it's just -- it's not realistic.
18 It's not how things work.

19 I will keep going back to the fact that,
20 from the point of view of the various pharmacopeias, who
21 are ultimately the regulating bodies that determine how
22 these assays are used, for them, the two assays are
23 equivalent. And, again, that means test the same
24 samples using either assay. They will give you the same
25 result.

1 And, you know, this is in an area where an
2 accurate result is extremely important. These are
3 antibodies that are being injected into people or
4 medical devices that are being placed in people. You
5 can't really afford to have wrong answers.

6 So if they saying they're equivalent, it
7 means they're equivalent to a pretty high tolerance.

8 BY MS. LOUGHRAN:

9 Q. Okay. Equivalent post-calibration to the
10 international standard; right?

11 A. Again, you can't run an assay without
12 having some calibrator for that assay. If what comes
13 out the other end of that assay is some sort of
14 numerical result or some sort of result that's not
15 relativistic; it's meant to be certain about something.

16 Q. Okay. Now, we talked about, you know, sort
17 of a series of percentages that were reported in these
18 publications. They were all around 90 percent; right?

19 A. That is correct. All of the numbers were
20 within about a percent of 90 percent, yes.

21 Q. And the size of Factor C was known to be
22 around, I think north of a thousand amino acids; right?

23 A. Correct. I believe the exact numbers are
24 1019 for one or two of the species, and I think it's
25 1020 for Limulus. I don't recall exactly, but those are

1 the numbers that stick in my head.

2 Q. So a 90.5 percent identity is about a
3 9-and-a-half percent difference; right?

4 A. Again, I will point to the language being
5 used here. Identity is a very specific term. And that
6 means where the amino acids are exactly the same; that
7 is, a less useful comparison term than similarity, that
8 takes into account both identity, as well as
9 functionally related amino acids.

10 Q. Okay. Well, again, I'm just going by the
11 numbers that were reported that you're citing in your
12 declaration. So if a POSA is looking at your numbers,
13 they're thinking there are about 100 differences in
14 amino acids.

15 Is that math correct?

16 A. That math is correct. There are about 100
17 differences in amino acids. But, again, we're talking
18 about identity. So the main thing that would strike a
19 POSA is that, you know, 90 percent -- 90-something of
20 the amino acids are exactly the same; not closely
21 related, but exactly the same.

22 So if you're starting with 90 percent
23 exactly the same, you can expect that the closely
24 related is going to end up somewhere near 100 percent.
25 So these are very, very closely related molecules from

1 an evolutionary perspective. Identity is a very high
2 bar.

3 Q. If you look at paragraph 104 of your
4 declaration, you cite a whole bunch of publications that
5 reported on sequences for different Limulus proteins;
6 right?

7 A. Correct.

8 Q. Okay. And none of these are reports of the
9 sequence for Limulus Factor C; correct?

10 A. Correct. None of them are Factor C. The
11 point of this was not to imply that there was a
12 sequenced -- a complete sequence of Factor C out there.
13 It was merely to counter Dr. Jain's assertion that it
14 was somehow difficult to obtain sequences from Limulus.

15 And this very long list shows that there's
16 no indication that it was difficult to obtain sequences
17 from Limulus. There were many published sequences for a
18 variety of different gene products.

19 Q. While there -- the field managed to
20 sequence a bunch of different proteins from Limulus, as
21 you list in this paragraph; right?

22 A. There were a bunch that had been published.
23 I am sure there was a longer list that had not been
24 published.

25 Q. Uh-huh. But for some reason, Factor C does

1 not show up on this list; right?

2 A. I think we've established through numerous
3 questions that, as of the priority date, there was no
4 publicly available, completely assembled published
5 sequence for either the protein or the mRNA for Factor
6 C. And I think we have also established that myself, or
7 any other POSA, would not attribute any specific reason
8 for that, given that there were a variety of
9 straightforward ways to very quickly obtain that
10 sequence.

11 And there are indications in the literature
12 that, in fact, there were several sequences out there
13 that were complete or nearly complete that simply had
14 not been publicly disclosed.

15 Q. Well, consistent with the fact that Factor
16 C, *Limulus polyphemus* Factor C doesn't show up on this
17 list, there was one group that was out there that was
18 saying it was difficult to obtain sequences for Factor
19 C; right?

20 MS. LO: Objection to form.

21 A. I believe you are referring to statements
22 made in the 498.

23 BY MS. LOUGHRAN:

24 Q. TCT, yes.

25 A. Okay. Those same statements, not word for

1 word, but the same general meaning is also present in
2 the European patent '670 that Dr. Frohman offered his
3 opinion about.

4 His assessment of those statements was that
5 he did not agree with those statements, that there was
6 nothing in particular that would have been difficult
7 about cloning the Factor C from Limulus. He was
8 speaking as of a priority date of October 2016.

9 I would simply say you can take the same
10 arguments he made, because there was no change in
11 technology, and equally apply that to December of 2013.
12 So I agree with Dr. Frohman's assessment of all those
13 statements that there was nothing difficult about it.

14 You know, as to why the authors said what
15 they said, I don't know the authors, so I cannot speak
16 to that. What I can say is nothing that they said is
17 anchored by any actual published facts that you can
18 point to.

19 Q. You do recognize that two of the authors in
20 the 498 PCT are the inventors on the '318 and '109
21 patents; right?

22 A. I do recognize that.

23 Q. Okay. And are you aware that the European
24 Patent Office has confirmed the inventiveness of the
25 claims in the '670 patent?

1 A. I do not specifically remember if I knew
2 the outcome of that challenge.

3 Q. So the European patent office did not agree
4 with Dr. Frohman, or at least believed that the
5 statements that the inventors made about recombinant
6 Factor C were true in order to allow them to have that
7 patent.

8 Does that change any of your opinions?

9 MS. LO: Objection to the premise of the
10 question, outside the scope.

11 A. The fact that the European office allowed
12 the patent does not speak to why they allowed the
13 patent.

14 BY MS. LOUGHRAN:

15 Q. So in your view, it would be consistent to
16 say that the inventors invented recombinant Factor C in
17 2016, and that also, separately say that they invented
18 it in 2013?

19 MS. LO: Objection, mischaracterizes,
20 outside the scope.

21 A. You're putting words in my mouth. I
22 congratulate the inventors on having their European
23 patent awarded with a priority date of 2016. They hold
24 that patent. That is all I will agree to.

25 BY MS. LOUGHRAN:

1 Q. If you look at paragraph 87, you say, "It
2 was known that all three zymogen proteins are serine
3 proteases and their cleavage activation site and
4 catalytic triad and substrate binding sites have been
5 characterized in the Tachypleus tridentatus Factor C and
6 Limulus polyphemus Factor C."

7 Do you see that?

8 A. I see that.

9 Q. Okay. Which reference or which exhibit are
10 you citing to there for the idea that Limulus polyphemus
11 Factor C's cleavage activation site and catalytic triad
12 and substrate binding site had been characterized?

13 A. I don't know the exhibits by number so
14 well, so we can look at them one at a time.

15 Q. Sure. So let's just -- we can do that. So
16 Exhibit 1022 is Tokunaga.

17 A. Uh-huh.

18 Q. Is it your contention that Tokunaga
19 characterized all of those things for Limulus
20 polyphemus?

21 A. Let me look at the exact data that are in
22 Tokunaga again. Certainly, you can make many
23 conclusions based on Tokunaga. I can see the other ones
24 as well.

25 Q. Yep. So I'll hand you Exhibit 1007. Is it

1 that one?

2 A. I didn't see them all.

3 (Exhibits 1007 and Exhibit 1016 were
4 introduced to the witness.)

5 BY MS. LOUGHRAN:

6 Q. And then here's Exhibit 1016. Actually,
7 that's my copy.

8 So I guess I can ask my question again.

9 A. Yes.

10 Q. Which of the cited references demonstrates
11 that it was known that Limulus polyphemus Factor C was a
12 serine protease, and its cleavage activation site in
13 catalytic triad and substrate findings site had been
14 characterized?

15 MS. LO: Objection to form.

16 A. Tokunaga is the reference that speaks most
17 directly to the function of Limulus Factor C. And from
18 the study of Tokunaga, we know the cleavage specificity
19 was indistinguishable from Tachypleus.

20 We know that it's a serine protease that
21 shows the same pattern of activation by chymotrypsin and
22 not by trypsin. We know that it binds a set of
23 substrates that are not distinguishable from Tachypleus.

24 So based on those findings, a POSA would
25 conclude that those two things are most likely, or with

1 a high degree of surety, the same between all three.
2 With regard to the catalytic triad, you know, again,
3 given the known level of homology, the known substrate
4 specificity and the behavior of the enzyme acted by
5 chymotrypsin, not by trypsin, that would give you a high
6 degree of surety that that catalytic triad is also the
7 same.

8 BY MS. LOUGHRAN:

9 Q. Well, I'm trying to understand, Doctor.
10 Because your testimony here, you're basically telling a
11 bunch of judges at the PTAB that all three zymogen
12 proteins, including Limulus, that their cleavage
13 activation site and catalytic triad and substrate
14 bindings sites had been characterized.

15 So I -- is that a true statement based on
16 those citations? Had they, in fact, been characterized?

17 MS. LO: Objection to form, argumentative.

18 A. It really depends on how you interpret the
19 word characterize. I would, for this paragraph,
20 interpret the word characterized as there were enough
21 similarities known between these enzymes, enough was
22 known about the homology between these enzymes that they
23 had been functionally characterized enough that a POSA
24 would conclude that these three parameters were, indeed,
25 identical between the enzymes between those species.

1 BY MS. LOUGHRAN:

2 Q. So you -- but you agree that Tokunaga
3 doesn't actually include direct information about what
4 the cleavage activation site and the catalytic triad of
5 Limulus Factor C; right?

6 MS. LO: Objection to form.

7 A. What Tokunaga includes is some limited
8 proteolytic sequence, but that limited proteolytic
9 sequence is very informative. We can see between Figure
10 7S and 8S that the N-terminal portion of those cleavage
11 sites have the same amino acid.

12 So we know that the protein is being
13 cleaved in a similar manner, because proteins of the
14 correct molecular weight to correlate with B chain, A
15 chain, L chain and heavy chain, have the expected
16 internal sequences.

17 Heavy chain is not relevant there because
18 there's not a cleavage site at the N-terminus. So we
19 know with a high degree of certainty that those cleavage
20 sites are present to produce the same chains. And from
21 what we know of the amino acids, the same substrate
22 specificity is being shown, and, also, from what we can
23 see of the high degree of homology between these
24 enzymes.

25 And while Tokunaga did not directly provide

1 sequence information for the catalytic triad, those
2 catalytic triad residues are highly conserved, not just
3 between Factor Cs, but between a diverse range of serine
4 proteases.

5 So it would be extremely improbable and
6 very surprising for any of those amino acids to be any
7 different, given that the known and sequenced Factor C
8 serine protease domains have that concerned catalytic
9 triad.

10 And then add to that that the Tachyplus
11 Factor C has the same serine protease activity with the
12 same substrates showing the same profile being activated
13 by chymotrypsin and not by trypsin.

14 BY MS. LOUGHRAN:

15 Q. Could you substitute any of the serine
16 proteases that you mentioned for Factor C and get the
17 same function?

18 MS. LO: Objection, outside the scope.

19 A. In my reading of paragraph 87, I don't see
20 anything about that.

21 BY MS. LOUGHRAN:

22 Q. Well, I'm not -- you just said that.

23 A. I don't want to speculate. I did not say
24 that.

25 Q. You just referenced serine proteases that

1 you said would provide a POSA with information
2 regarding --

3 A. Serine proteases --

4 MS. LO: Objection, mischaracterizes.

5 A. Serine proteases share conserved residues
6 in the catalytic triad. They work by a very similar
7 biomechanical mechanism. That doesn't mean they all
8 have exactly the same substrate specificity.

9 But the three amino acids of the catalytic
10 triad are essentially invariant between serine
11 proteases. It's just part of how they work. But part,
12 it's the cleavage part.

13 BY MS. LOUGHRAN:

14 Q. But Tokunaga doesn't say anything about the
15 proteolytic triad for *Limulus polyphemus*; right?

16 A. Tokunaga presents a lot of data that
17 pertained to the protease function. But as far as the
18 catalytic triad, I don't recall Tokunaga talking about
19 that specifically.

20 Information about the catalytic triad is a
21 conclusion that a POSA would draw as of the priority
22 date based on the vast amount of additional literature
23 that was available by the priority date.

24 Q. So for that assertion in paragraph 87,
25 you're not relying on these cited references, you're

1 relying on the knowledge of a POSA?

2 MS. LO: Objection, mischaracterizes.

3 A. I stand by the text that is written in
4 paragraph 87. I believe for the entirety of what I
5 describe in my declaration, the assumption is that all
6 of it would be -- all of it characterizes everything
7 from the point of view of a POSA at the priority date.

8 BY MS. LOUGHRAN:

9 Q. Dr. Schaefer, by 2013, the field knew how
10 to -- or it was known in the field how to produce a --
11 like an endotoxin detection agent; right?

12 A. Can you be more specific, what you mean by
13 it was known in the field? And are we talking about an
14 endotoxin agent that would be certifiable as a component
15 in a kit? Or are we just talking about in general, a
16 reagent that would be competent for the detection of
17 endotoxin.

18 Q. The latter. By 2013, scientists in this
19 field, the scientists that we've been talking about who
20 are authors of this publication, knew how to create an
21 agent to detect endotoxin; right?

22 A. A POSA, based on the available literature,
23 would be able to read the great quantity of literature
24 and produce a reagent that can detect endotoxin. Yes,
25 and that's true by that priority date.

1 Q. By 2013, a POSA also could produce an
2 endotoxin detection agent recombinantly; right?

3 A. Yes. Also, from the literature, there was
4 adequate description of, certainly, the enzymes from
5 Tachypleus and Carcinoscorpius to produce an endotoxin
6 detection assay.

7 And also based on the ability to produce
8 the Factor C from Limulus based on the information that
9 was out there, one could first clone the Limulus Factor
10 C and also produce an assay that was based on Factor C
11 from Limulus recombinantly.

12 Q. And it was known how to -- if you -- let's
13 say some of the publications we've been talking about
14 are recombinant Factor C from Carcinoscorpius. It was
15 known how to express that recombinant protein into a
16 solution and gather the proteins from that solution;
17 right?

18 A. I would ask you to be more specific in your
19 question. What are you referring to?

20 Q. Well, that you would have -- there's some
21 difference between proteins that are not secreted. We
22 can talk about those. But there was the ability to
23 recombinantly produce Factor C in a secreted form and
24 collect those proteins from a solution; right?

25 A. As per my recollection, the descriptions of

1 production of recombinant Carcinoscorpius Factor C were
2 in soluble form.

3 Q. And so those would be collected from a
4 solution like a supernatant or something?

5 A. A supernatant would be recovered. And
6 depending on the concentration of Factor C, you know,
7 supernatant might be used directly, it might be
8 dialyzed, it might be concentrated; any number of things
9 could happen.

10 But, basically, yes, the Factor C in the
11 solution could be used to measure endotoxin in the
12 context of an endotoxin assay.

13 Q. And that was known by 2013?

14 A. As I recall, it was known by 2013, yes. I
15 believe there were several kits on the market, and those
16 kits were based on publicly available or published
17 information, as I recall.

18 MS. LOUGHRAN: Okay. All right. Let's
19 take a quick ten-minute break. I want to gather my
20 thoughts and see where we are.

21 (A break was taken.)

22 BY MS. LOUGHRAN:

23 Q. Hello again, Dr. Schaefer. How are you?

24 A. I'm good.

25 Q. All right. I want to go back -- we were

1 looking around paragraphs 86 and 87. Yeah, paragraph
2 85. So you say at the end of that paragraph, "Key
3 regions in coding functional units of each enzyme and
4 motifs for interactions between partner proteins would
5 be highly conserved across species."

6 Do you see that?

7 A. Yes.

8 Q. Okay. Now, when you talk about that,
9 you're referring to the sequences of the -- the native
10 proteins, right, that you would then use to make
11 recombinant proteins; right?

12 A. I don't see a reason for making that
13 distinction if we're talking about the Factor C
14 proteins, without any sort of introduced modification.
15 The sequence of the native protein and the recombinant
16 protein would be identical.

17 Q. Okay. But you're making a link between the
18 conservation of those sequences and the function of the
19 protein; right?

20 A. I guess I would ask you to be a little more
21 specific in your question.

22 Q. Okay. You could have a recombinantly
23 produced Factor C protein --

24 A. Yes.

25 Q. -- that has the same sequence as the native

1 protein; right?

2 A. Yes.

3 Q. And that recombinantly produced protein
4 could have a different, for example, residual activity
5 relative to that native protein; right?

6 A. That is correct. That is, in fact, what
7 the inventors showed, so I agree with that statement.

8 Q. Okay. And so the difference there in
9 activity is not attributable to the sequence; right?

10 MS. LO: Objection, form.

11 A. The question you ask does require some
12 degree of speculation, because if we're just talking in
13 a very abstract way about, you know, any native protein
14 versus any recombinant protein, there could be things
15 that occur, like perhaps the recombinant protein gets
16 clipped by a host protease, and now the sequence is
17 actually different between the recombinant protein and
18 the expressed protein. So there can be exceptions to
19 what you have just asked me.

20 BY MS. LOUGHRAN:

21 Q. Okay. Would it be fair to say that if you
22 see a difference in the recombinantly expressed protein,
23 it could be because of a sequence difference or because
24 of some other reason?

25 A. Again, if we're talking in very abstract

1 terms, I agree with that statement, yes. It could be
2 either a sequence in difference -- a sequence difference
3 that's due to some sort of posttranslational
4 proteolysis. Or it could be for another reason, such as
5 some sort of post-translational modification that
6 differs between the recombinant protein and the native
7 protein.

8 Q. And the inventors in the '318 patent, for
9 example, theorized that the reason why they were seeing
10 different residual activity through recombinant Factor C
11 and mammalian cells relative to native or insect cells
12 was, as you mentioned, a post-translational
13 modification; right?

14 A. That was a particular theory that they
15 articulated at a given point in time, perhaps even
16 multiple points in time. Yes, as you said, a theory.

17 Q. So that theory, the post-translational
18 modification theory, didn't attribute the difference in
19 residual activity to a difference in Factor C amino acid
20 sequence; right?

21 A. The -- assuming we're talking about the
22 same theory, the authors articulated a theory at one
23 point that was based upon a post-translational
24 modification. And that theory did not include anything
25 like a protease clipping that would have changed the

1 sequence, yes, we can agree to that.

2 Q. Okay. If you turn to paragraph -- let's
3 see -- paragraph 107 of your IPR declaration, so now you
4 are discussing your opinions with respect to the
5 enablement of Claim 21 of the '318 patent; do you see
6 that?

7 A. I do.

8 Q. Okay. And you disagree with Dr. Jain's
9 assertion regarding the breadth of Claim 21; right?

10 A. Correct.

11 Q. Okay. Now, do you agree that Claim 21
12 covers a Factor C protein recombinantly produced by HEK
13 cells from Limulus polyphemus that has a residual
14 activity in sodium citrate of 11 percent?

15 A. Can we look back at Claim 21 again?

16 Q. Sure. It is produced in your declaration
17 or you can look at the patent.

18 A. If I can find the patent again, I'll look
19 at it there.

20 Q. Yes. Right there.

21 A. Okay. It sets a threshold value of
22 10 percent or higher. So 11 percent, I agree, is higher
23 than 10 percent.

24 Q. Okay. And similarly produced protein that
25 had a value of 99 percent for residual activity in the

1 presence of sodium citrate would also fall within the
2 scope of that claim; right?

3 A. Again, it's a threshold value. So any
4 number that you read to me that's 10 percent or greater
5 is going to be within the scope of that claim. But,
6 again, it's a threshold value. It's not a range that
7 was defined, it was a threshold. So it's a binary
8 decision, either it is or it isn't.

9 Q. And you agree that a residual activity of
10 even greater than 100 percent, in the presence of sodium
11 citrate, would meet that claim; right?

12 A. Well, again, I will recite the claim. The
13 claim says 10 percent or higher in the presence of 20
14 millimolar sodium citrate. So it's a threshold value,
15 and any value that's higher than threshold value is
16 within the claim.

17 Q. And so your contention is that 10 percent
18 or higher is not a range; is that true?

19 A. It's not a range; it's a threshold.

20 Q. How is a threshold different than a range?

21 A. By its very definition, a range specifies
22 two endpoints and says anything in between those two
23 endpoints is what is encompassed.

24 The threshold, again, is a binary term. We
25 have something that is either greater than or not

1 greater than. It's not a range.

2 Q. Is it because the threshold doesn't have an
3 upper bound?

4 MS. LO: Objection to form.

5 A. A threshold is different from a range. A
6 range is, yes, bounded by two ends. A threshold is
7 simply a value that is set as either, you know, greater
8 than or less than.

9 BY MS. LOUGHRAN:

10 Q. Okay. I'm just trying to understand your
11 opinion. If your opinion is that it's not a range
12 because it doesn't have an upper bound, is that your
13 opinion?

14 MS. LO: Objection, asked and answered.

15 A. As I have said, these two different terms
16 have different definitions. A range has an upper and
17 lower bound.

18 A threshold is simply a binary
19 characteristic. Something meets a threshold or
20 something does not meet the threshold. They're
21 intrinsically different.

22 BY MS. LOUGHRAN:

23 Q. Okay. If the claim recited 10 percent to
24 100 percent, you would count that as a range; right?

25 A. I would count that as a change.

1 Q. Okay. If I had a Factor C protein produced
2 by HEK -- recombinantly produced in HEK from Limulus
3 polyphemus that had a residual activity of 101 percent,
4 that Factor C protein would not fall within the scope of
5 the 10 to 100 percent range; correct?

6 A. That is correct. It would be outside of
7 the range.

8 Q. Okay. But with respect to Claim 21, that
9 Factor C protein would fall within the scope of Claim
10 21; correct?

11 A. It falls within the scope because it's a
12 number that's 10 percent or higher.

13 Q. So a range would be narrower than what's
14 actually claimed in Claim 21?

15 MS. LO: Objection to form.

16 A. There are different -- they're just
17 different by nature. And so if they're different by
18 nature, I don't want to compare them quantitatively.
19 You know, a range is a range; a threshold is a binary
20 decision.

21 BY MS. LOUGHRAN:

22 Q. Okay. Dr. Schaefer, have you seen anything
23 in the '767 application, as written, that explains why
24 recombinant production of Factor C in mammalian cells
25 gives a higher residual activity than native or

1 recombinant production of Factor C in Sf9 insect cells?

2 A. I do not recall seeing an explanation or a
3 mechanism, but my understanding is that an explanation
4 or a mechanism is not required in order for the feature
5 that is being described as patentable to make it
6 patentable. We don't have to know why it happens.

7 Q. But if a POSA wants to make a Factor C --
8 recombinant Factor C protein in HEK cells that falls
9 with -- above the threshold, as you use the term in the
10 claim, does the patent -- does the '767 application tell
11 them how to do that?

12 A. The '767 teaches that if you produce HEK
13 293 -- sorry -- if you produce Factor C in HEK 293 cells
14 or in CHO-DG44 cells, you will get a Factor C that has a
15 higher residual activity than the Factor C that is
16 produced in either insect cells or the native protein
17 that's used in the LAL assay.

18 Q. And is that true in all cases; is that
19 necessarily true?

20 MS. LO: Objection to form.

21 A. I don't know that your question is
22 answerable. It is so broad and open-ended. For
23 example, if I take my Limulus Factor C and I boil it,
24 that statement will no longer be true.

25 So, certainly, there are a whole range of

1 circumstances that one could dream up under which that
2 statement would no longer be true.

3 BY MS. LOUGHRAN:

4 Q. But in your hypothetical, the '676
5 application doesn't say, "Don't boil your recombinantly
6 produced Limulus polyphemus Factor C"; right?

7 A. The '767 does not give any kind of list of
8 things not to do with Limulus Factor C.

9 Q. Dr. Schaefer, you -- earlier we talked
10 about the inventor statements in the 498 PCT; right?

11 A. Correct.

12 Q. And you essentially indicated that those
13 statements were incorrect; is that fair?

14 MS. LO: Objection to form.

15 A. I don't recall saying those words.

16 BY MS. LOUGHRAN:

17 Q. Well, let's look at the 490 PCT.

18 (Exhibit 1005 was introduced to the
19 witness.)

20 BY MS. LOUGHRAN:

21 Q. So you've been handed Exhibit 1005, it's
22 the -- we've been referring to it as the 498 PCT. Do
23 you recognize this document?

24 A. I do.

25 BY MS. LOUGHRAN:

1 Q. And if you look at the first page, the
2 cover page, it's on sort of the second page of the
3 document. It lists Hikaru Mizumura and Toshio Oda were
4 both inventors on the '318 and '109 patents; right?

5 A. Yes, I see that.

6 Q. And I think you talked about how
7 Dr. Frohman had opined on the statements that the
8 inventors made in this publication; right?

9 A. He had some opinions related to the notion
10 that you might construe things the inventors say that
11 could have implied to a person reading it that it might
12 be difficult or might have been difficult to have cloned
13 Factor C.

14 And he very much disagreed with those
15 assertions, saying that he thought it would be
16 straightforward to clone it. He listed several ways of
17 cloning Factor C from Limulus.

18 And I agreed with his assertions that not
19 only would there be no reason to expect it to be
20 difficult, but there are multiple reasons to expect it
21 would be straightforward and multiple protocols one
22 could have followed to clone Factor C from Limulus, both
23 as of the priority date he was discussing, which was in
24 October of 2016, and the priority date that we are
25 discussing, which was in December of 2013.

1 Q. Okay. You realize that the inventors
2 submitted this document to multiple patent offices
3 around the world; right?

4 A. Yes. I believe I know that this document
5 or a closely related document was submitted in both
6 Japan and the US, similar form. And then I don't know
7 how the European document discussed by Dr. Frohman was
8 related, other than it definitely contained very similar
9 statements, and it was in a similar time frame.

10 Q. Do you -- is it your opinion that the
11 inventors were accurately portraying the difficulty of
12 Factor C as they viewed it at the time, or that they
13 were making a misrepresentation?

14 MS. LO: Objection, mischaracterizes,
15 outside the scope.

16 A. I don't know the inventors. I did not know
17 the inventors at the time they wrote what they wrote.
18 Nothing that they wrote is anchored by any facts. There
19 are no publications that are called out. There, as far
20 as I recall, are no references in those sections to
21 previous patents, so it's a preamble of unclear
22 significance.

23 BY MS. LOUGHRAN:

24 Q. Would a POSA -- well, let me strike that.

25 Do you look with skepticism on the

1 remainder of this publication?

2 MS. LO: Objection, form, outside the
3 scope.

4 A. We're talking about the 498 document?

5 BY MS. LOUGHRAN:

6 Q. Yeah.

7 A. The -- much of the remainder of the 498
8 document contains data, so myself and a POSA would look
9 at data and take it at face value. The data appear to
10 be of good quality.

11 Then there are also the claims. There are
12 no opinions or relativistic descriptions in the claims
13 themselves. So as a whole, I think that this is a very
14 high quality document, and I think a POSA would agree
15 with that.

16 The part that I place less value on are the
17 statements that are not anchored by reference to
18 figures, reference to publications, references to
19 previous patents. Again, these are descriptions, in
20 some cases, opinions that use a lot of adjectives, and
21 they're not anchored to specific facts.

22 Q. So if you look at paragraph 12. When the
23 inventors say, "In *Limulus polyphemus*, even though more
24 than 20 years have passed since the report in the genus
25 *Tachypleus*, complete identification of these proteins

1 and genes in terms of both structure and function has
2 not been achieved."

3 Do you see that?

4 A. I do see that.

5 Q. Okay. Do you -- do you disagree with the
6 inventor's statement there?

7 MS. LO: Object to the form, outside the
8 scope.

9 A. I don't know how to interpret the
10 statements of the inventors because it's fairly vague.
11 You know, what do they mean by "complete
12 identification"?

13 Do they mean that the complete sequence, as
14 far as every single nucleotide and every single amino
15 acid had not appeared in a peer-reviewed publication,
16 then, yeah, it's an accurate statement. You know,
17 there's many ways to interpret what they have said
18 there.

19 If what they're saying is the complete
20 sequence, as I described it, every single nucleotide,
21 even amino acid in fully assembled form, had not
22 appeared in a peer-reviewed publication, it's an
23 accurate statement.

24 BY MS. LOUGHRAN:

25 Q. Okay. And when you look at paragraph 16 on

1 page 3; do you see that?

2 A. Uh-huh.

3 Q. They say, "An object of the present
4 invention is to provide all full-length recombinant
5 proteins involved in the coagulation mechanism of
6 Limulus polyphemus cDNAs in coding these proteins and
7 uses thereof."

8 Do you see that?

9 A. I do see that.

10 Q. Do you agree that that is the invention
11 that they described in this patent application?

12 MS. LO: Objection, outside the scope.

13 A. I think we have to look at the claims one
14 by one and evaluate what the invention is that way.
15 This is not one of the claims; this is preamble.

16 BY MS. LOUGHRAN:

17 Q. If that information, the full-length
18 recombinant proteins involved in the coagulation
19 mechanism of Limulus polyphemus already existed, would
20 it be an invention for the inventors to secure?

21 MS. LO: Objection, outside the scope,
22 incomplete hypothetical.

23 A. I'm not a patent lawyer. It's not up to me
24 to judge what qualifies as an invention or not. Again,
25 I think we need to look at the claims one by one to see

1 what is claimed.

2 BY MS. LOUGHRAN:

3 Q. Do you believe that the inventors in this
4 patent application described comparing the endotoxin
5 detection activity of recombinant *Limulus polyphemus*
6 using the sequences that they had obtained to that of
7 recombinant *Tachypleus* Factor C?

8 MS. LO: Objection, foundation, outside the
9 scope.

10 A. Can we look at the specific data?

11 BY MS. LOUGHRAN:

12 Q. Sure. So if you turn to paragraph 186, so
13 they have an example here, "activity comparison with
14 recombinant Factor C from *Tachypleus*"; do you see that?

15 A. Yes.

16 Q. Did you review this in preparation of your
17 declaration?

18 MS. LO: Objection, vague.

19 A. I've reviewed all of the documents. Do I
20 remember every single detail of every single document,
21 not necessarily. But, again, if we can look at the
22 specific data, not a paragraph summarizing the data, we
23 can speak about it in more detail, if you'd like.

24 BY MS. LOUGHRAN:

25 Q. Okay. I'm going to strike the line of

1 questions, but we can put that one away.

2 You opined on the obviousness of the claims
3 of the '318 patent, for example, at page 58 of your '318
4 declaration; do you see that?

5 A. Yes, I see that section.

6 Q. Okay. Do you have an understanding of the
7 difference between obviousness and written description
8 and enablement?

9 A. I would prefer to read the exact
10 definitions that are included in my declaration that is
11 a response to your question.

12 Q. Okay. Well, in paragraph 125 of your
13 declaration, you say that "Dr. Jain argues that by April
14 of 2019, POSAs would have reasonably expected to
15 successfully generate recombinant Factor C of the
16 Limulus polyphemus species via HEK293 cells, where that
17 recombinant Factor C, as a residual activity, falling
18 within the range defined in Claim 21."

19 And you say, "In my opinion, this opinion
20 cannot be reconciled with Dr. Jain's lack of written
21 description and enablement support in the '676
22 application."

23 Do you see that?

24 A. Yes.

25 Q. Okay. So what is your opinion based on?

1 A. That Dr. Jain makes two completely contrary
2 arguments. And the only thing that's different in his
3 mind is of the two time frames, one being the priority
4 date and the other being April 2019, is now we know the
5 sequence, the full sequence, the fully assembled
6 sequence of recombinant Factor C, based on McClymont and
7 based on the disclosure of the inventors themselves in a
8 similar time frame; all right?

9 But, you know, as I have shown, the
10 complete sequence of Limulus Factor C could have easily
11 been derived back on the priority date.

12 So Dr. Jain argues that in 2013, because we
13 didn't have the sequence, you couldn't possibly
14 determine any of these things. Suddenly in 2019, now
15 that we have the sequence, now we can predict exactly
16 what the residual activity would be, what other
17 properties would be.

18 So the arguments that he makes are
19 completely contradictory.

20 Q. So because you have articulated your
21 position that a POSA could have gotten the sequence as
22 of 2013, do you agree that Claim 21 would have been
23 obvious at that point?

24 MS. LO: Objection, outside the scope, now
25 we're talking about the claim.

1 A. You're putting words in my mouth. I didn't
2 offer an opinion about that.

3 BY MS. LOUGHRAN:

4 Q. Well, you said the only difference between
5 Dr. Jain's opinions is the obtaining of the sequence;
6 right?

7 A. What I said is he's making two different
8 arguments. In one case, he says, we couldn't have
9 gotten the sequence and not only that, but even if you
10 had the sequence, you wouldn't have known what Factor C
11 would do, how it would behave in residual activity
12 assays.

13 Now suddenly, in 2019, oh, we have the
14 sequence. And because we have the sequence, we know how
15 Limulus Factor C would behave in these residual activity
16 parameters.

17 So, you know, it's the -- it's completely
18 different arguments that are mutually opposed. And the
19 thing I pointed out is the only difference in time
20 frames, from his perspective, is in one case, we knew
21 what Factor C was; in the other case, we didn't yet know
22 what Factor C was.

23 So there's no logical reason that he would
24 have completely turned his arguments around.

25 Q. Well, this is why I asked you originally

1 the difference between obviousness and written
2 description enablement. Do you have an understanding
3 that to describe -- adequately describe an invention,
4 you have to describe your possession of the full scope
5 of that invention?

6 MS. LO: Objection to form.

7 A. Again, we can read out how these terms are
8 defined in my declaration. I would rather not
9 paraphrase them off the top of my head.

10 BY MS. LOUGHRAN:

11 Q. Well, I can't ask you the question, because
12 you can look at your -- the standard for written
13 description, which appears at page 4.

14 A. I see it.

15 Q. Okay. I guess my question to you is the
16 same one: Do you have an understanding that, in order
17 to adequately describe an invention, you have to provide
18 enough description to a POSA to understand that you're
19 in possession of the full scope of that claim?

20 MS. LO: Objection to form.

21 A. Reading what is in my declaration, I
22 understand that to satisfy the written description
23 requirement of the patent's disclosure, including the
24 specification, figures and claims must convey to persons
25 of ordinary skill, in other words a POSA, that the

1 inventor invented what is claimed.

2 In other words, after an objective inquiry
3 into the four corners of the patent document, the
4 perspective of person of ordinary skill, that person
5 would recognize that the inventor was in possession of
6 the claimed subject matter as of the effective filing
7 date of the patent.

8 So I believe we have said fairly similar
9 things using different words.

10 BY MS. LOUGHRAN:

11 Q. And then with respect to obviousness, if
12 a -- if it were shown that it would obvious to make
13 recombinant Factor C from HEK cells with respect to --
14 well, let me strike that.

15 All right.

16 MS. LOUGHRAN: Can we take a quick break?

17 (A break was taken.)

18 BY MS. LOUGHRAN:

19 Q. Hi, again, Dr. Schaefer.

20 A. Hello.

21 Q. Have you spoken with your counsel about the
22 substance of any of your testimony during any of our
23 breaks today?

24 A. Not at all.

25 Q. Dr. Schaefer, I don't have any other

1 questions for you on the '318 IPR.

2 A. Okay.

3 Q. I think I'll allow your counsel to reserve
4 any redirect when we finish up on the PGR tomorrow, if
5 that's okay with you.

6 MS. LO: Yes.

7 MS. LOUGHRAN: And that's all the questions
8 I have for you.

9 (The proceeding adjourned at 4:55.)

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ability 7:1 15:19 68:9 72:15 73:10 76:13 117:12 132:12 197:7,22 220:9 able 53:1 72:3,11,12 75:17 90:21 107:12 109:20,25 117:22 147:8 151:21 155:22 171:11 196:23 absence 81:22 absolute 55:24 absolutely 39:1 68:1 75:9 121:17 absolutes 108:8 121:10 absorb 147:20 abstract 182:9 200:13,25 academic 20:12 accept 81:4 accepted 74:14 178:19,20 accessible 92:6 accomplish 98:8 110:1 account 89:1 101:23 113:17 114:17 140:19 161:20 185:8 accuracy 13:19 accurate 6:7 15:18 20:7 32:6 59:14 65:16,17	66:18,19 85:6 139:14 160:8,18 184:2 211:16,23 221:5 accurately 136:4 209:11 achieve 81:24 achieved 211:2 acid 52:16 69:10,11,16,16 70:13 71:12,16 72:19 73:3 104:4 111:15 114:20 115:9,10,20,21,23 115:25 116:13,19 118:8 120:2 121:3 121:14 122:9 133:4 133:17,23 134:1,12 134:20,25 135:4,5,9 135:23 136:6,11 137:2,5,9 138:12,17 138:18 140:13,20 140:25 143:3 148:20,25 149:3 151:5 152:8 171:2 172:2 175:13 193:11 201:19 211:15,21 acids 68:23 71:2 113:17 114:18 115:3 116:8 121:17,19,20 135:25 138:22 148:12 171:15 184:22 185:6,9,14 185:17,20 193:21 194:6 195:9 acid-by-amino 135:23 acknowledge 38:1,4 68:17 70:2 107:8,11 108:7 115:16 118:17 119:22 142:10	acknowledged 144:17 acted 192:4 acting 68:13 action 220:12,16 activate 142:24 activated 174:6 194:12 activates 147:21 167:20 activation 21:7 41:6,6,7 83:18 142:18 145:22 190:3,11 191:12,21 192:13 193:4 activities 55:20 76:4 77:19 78:11 79:4 84:15,19 84:21 153:21,25 174:10 176:12,21 activity 19:4 40:13,16,17,25 41:4,20,24 49:14 50:3,13,17,22 51:5 51:11,13,16,22,23 54:11,16 55:15 56:17,18 57:15,21 58:10,17,23,24 59:2 59:4,5,8,11,12,17 60:5,11,15,17,24 61:7,10,22 62:5,16 62:22 63:14,24 74:8 74:9,11 75:23 76:5 78:25 79:10,13,23 79:24 80:1,20 81:10 81:10,19 82:25 120:22 121:15 122:19 132:8,10,19 142:19 144:12,19 144:21,23 145:18 145:25 147:9 152:23 154:15	155:23 156:3,3,4,13 167:14,16,20 171:7 175:18 194:11 200:4,9 201:10,19 202:14,25 203:9 205:3,25 206:15 213:5,13 214:17 215:16 216:11,15 actual 47:20 96:8 104:4 123:19 136:19,20 139:6 163:6 175:13 182:22 188:17 adaptive 20:15 add 22:10 23:8 64:8 68:6 120:19,23 123:11 124:2 155:9 194:10 adding 135:25 addition 68:6 151:10 172:4 additional 195:22 adequate 44:8,12 197:4 adequately 217:3,17 adjectives 210:20 adjourned 219:9 adjusted 36:7 adjustments 55:13 admin 148:13 150:22 adopt 124:8,10 adopted 33:9 advantageous 159:20 affect

69:6	algorithm	121:14,16,19,20	51:2,3 53:22 69:3
afford	111:14,25 113:23,24	122:9 133:4,17,23	70:5 72:21,22 73:6
184:5	114:23,24 115:2,7	134:1,12,20,25	76:7,21 78:22 80:8
afforded	115:11 116:3,10,19	135:4,5,8,23,25	80:10,22 83:25
33:18,19 34:1	117:10,12,24	136:6,10 137:1,5,9	84:17 89:10 100:13
afternoon	118:10,21 122:22	138:12,17,18,22	136:9 152:21
131:9	123:1,2,4,5,9,9	140:13,19,25 143:3	157:14 158:7
age	126:7,8,10 127:24	148:12,20,25 149:3	176:25
85:16	129:7	151:5 152:8 171:2	answerable
agent	align	171:15 172:1	206:22
196:11,14,21 197:2	117:12 128:19	175:13 184:22	answered
agnostic	alignment	185:6,9,14,17,20	19:22 38:23 45:14
22:12 98:11 123:2	111:2,11 128:9,9	193:11,21 194:6	46:20 51:1 70:4
ago	141:6	195:9 201:19	76:18 84:18 136:14
6:13,17	aliquot	211:14,21	136:15 204:14
agree	103:12	amount	answering
20:2 29:21 31:13,15	allow	66:7,8 109:2 146:10	9:24
31:17 40:12 44:25	73:11,12 86:14 171:3	167:25 181:4	answers
48:10 52:15,19 53:3	189:6 219:3	195:22	8:4,7 184:5
57:13 60:21 62:8	allowed	amplification	antibodies
69:9 71:16 72:17	72:9 189:11,12	110:13	71:13,22,23 72:5
77:13 78:19 79:12	allows	amplify	184:3
88:19 92:16 94:4	157:25 182:21	103:12 106:25 136:1	antibody
96:2 103:9 130:5,9	alpha	analysis	73:2 178:22
135:11 136:21	142:5 147:20	42:15 90:22 97:6,12	anticipate
138:24 139:2	altered	98:24 102:25 104:7	66:9 81:11,14
141:18,20 143:2	73:17,17	107:23 117:6 120:6	antigen
144:8 145:25	alternate	123:8,11 126:6,6,12	18:22
155:21 164:13	36:2 55:22	134:8 135:2 160:16	anybody
165:3,14,22 181:16	alternative	analyze	12:13 96:3 126:5
182:8 188:5,12	53:14 101:1,2 106:10	129:21	anymore
189:3,24 193:2	Alwis	anchored	150:18
200:7 201:1 202:1	2:15,19 156:18	188:17 209:18	anyway
202:11,22 203:9	164:14 169:22	210:17,21	75:10 134:15 156:8
210:14 212:10	172:17	and/or	APPEAL
215:22	American	221:6	1:2 3:2
agreed	143:23 163:25	animals	appear
3:10 9:1 89:19	amino	64:14 66:3,5	13:7 32:22 40:5,15
144:22 208:18	52:16 68:23 69:10,11	annotated	42:19,25 44:2 47:21
agreement	69:16,16 70:13 71:2	111:23	62:14 63:17 112:12
10:16	71:12,16 72:19 73:3	answer	155:17 210:9
air	104:4 111:15	6:25 7:6,15,19,21,23	APPEARANCES
101:1	113:17 114:18	7:24 9:24 19:19,23	4:1
al	115:3,9,10,20,21,23	19:25 33:22 37:5,9	appeared
2:14 65:1 86:1	115:25 116:8,13,19	37:23 38:16 46:15	211:15,22
179:15	118:8 120:2 121:3	46:21 49:5,6 50:21	appears

57:11 61:10,14 94:25 95:1 155:1,3 162:9,17 163:16,18 175:6 180:20 217:13 220:7 apples 171:21,22 172:7,7,15 172:15,17 apples-to-apples 154:9 167:4 172:12 173:5 apples-to-oranges 87:9 applicable 50:20 51:6 applicant's 58:3 application 2:8,14 31:8 43:19,25 44:3,8,12,17,21 45:1,4,12,17,19 46:2,4,17,24 47:1,4 47:5,8,14,19,22,24 48:9,11,22,23 50:2 50:14,23 52:15,15 52:18 53:5,10,18 56:5,16 57:2 58:3,7 63:12,19,24 77:12 93:10 104:3 105:13 115:17 159:12 160:2 205:23 206:10 207:5 212:11 213:4 214:22 applications 26:23 applied 46:8 50:8 apply 38:19 39:2,8,11 145:7 188:11 appreciable 141:3 144:9 appreciate 83:25 approach	106:22 108:25 approached 8:25 9:5,9,15,21 approaches 107:4,9,13 appropriate 41:8 175:9 approximately 9:4 66:25 April 214:13 215:4 arachnid 98:15 Archive 95:12 area 97:15,16 184:1 areas 29:12 arguably 129:13 argue 121:25 argues 142:25 214:13 215:12 argumentative 192:17 arguments 35:15,16 188:10 215:2,18 216:8,18 216:24 array 75:21 arrive 53:1 104:16 106:11 107:6 arrived 85:2 102:25 105:8 107:23 art 25:23 26:3 27:8 31:9 31:14,16,20 33:3 35:9,20 91:1 96:16 117:21 133:4 147:7 article	2:10,13,15,17,18,19 2:21,22 29:23 30:6 30:7,18,21,22 31:2 64:25 66:10 71:8,10 71:15,20 85:25 88:2 88:15 131:16,18 156:18 articles 30:25 162:20 articulated 201:15,22 215:20 ascribe 167:14 Asian 52:23 66:23 asked 38:22 45:14 46:20 51:1 70:4 76:18,19 136:13 200:19 204:14 216:25 asking 20:1 35:13,23 47:23 49:7 61:24 80:12 111:9 126:19 127:1 135:7 138:15 140:22 142:15 147:11 173:3 174:1 178:10 aspartic 114:20 aspect 50:7 79:13 80:3,5 aspects 167:10 assay 22:18,20 74:23 79:24 82:1,13,13 83:16 84:8,8 85:8,9,11,13 85:14,21 89:8 100:3 100:12 104:18 119:9 120:21 122:19 134:10 135:8,19,23 136:1,3 145:1 147:12 160:14 168:2 173:18,19 177:6,7	177:23 178:5,6,15 178:15,18,19,23,25 179:7,11 181:22 182:10,11 183:24 184:11,12,13 197:6 197:10 198:12 206:17 assayed 160:22 assays 23:21 42:12 74:13 81:9 84:7 154:2 159:19 171:8 173:15 174:23 175:9 176:5 177:5,7 180:5,14 182:1 183:17,22,22 216:12 assemble 31:25 92:8 94:7 96:17,19,20 97:4 99:2,11 100:6,9 101:20 102:22 103:4,15,25 109:20 110:8 assembled 32:12 46:13 93:24 94:16 98:13 99:7 103:1,6,7 104:10,11 187:4 211:21 215:5 assembling 97:2 100:8 103:17 107:14 assembly 92:3 94:4 assertion 186:13 195:24 202:9 assertions 208:15,18 assessing 159:10 assessment 66:18 176:23 188:4 188:12 assistants 14:12
--	--	---	---

assisted 21:19	188:14,15,19 196:20 201:22	142:15 146:13 148:4 149:20	195:22 196:22 197:7,8,10 198:16
assisting 14:9	author's 99:16 162:11	158:22 168:19 181:10 183:19	201:23 214:25 215:6,7
associated 6:11 102:5 115:12 145:12	available 19:14 24:1 31:24 32:11,14 53:12 92:8	198:25 202:15 215:11	basic 145:3
assume 7:6 115:12,13 157:19 157:25 158:2,6	92:12 95:25 117:2 174:22 187:4 195:23 196:22 198:16	backbone 142:3	basically 32:21 34:17 51:15 125:14 192:10 198:10
assuming 110:4 158:1 201:21	Avenue 4:5	backbones 141:25 142:8	basis 166:23
assumption 18:12 38:24 196:5	awarded 189:23	background 25:8,9 26:15,16 27:1 27:9,12 28:1,10,24 65:25	BCL10 21:9,10 70:25
asterisk 111:16	aware 10:25 11:2,23,25 12:21 13:24 15:23 27:3,5 32:7,9 36:1,4 36:9,18,20,23 63:23 91:4,23 92:17,21,23 93:21 94:12,14 99:18 105:18 122:6 141:15 157:15 188:23	backgrounds 26:2	BC110 21:7
Atlantic 4:5	awareness 12:1 38:6 48:16,18 51:10 99:23	bacteria 75:17,19	becoming 29:20
atomic 183:10	axis 146:20,23	bacterial 75:16,21	began 5:1
attach 73:10,11	a.m 5:1	bacterium 98:15	beginning 80:13 88:8 119:1 141:11 144:17 161:3
attached 2:25	B	bar 61:15 62:18 81:23 186:2	begins 25:22
attachment 145:11	B 20:15,15 98:22,25 99:6,10 100:14,15 110:18 137:22 138:17 139:5 140:10 146:8 148:21 193:14	bars 62:8 154:15 180:23	behalf 1:12 3:13
attempting 70:24		base 16:20	behave 80:24 120:21 144:13 171:24 172:9 216:11,15
attention 86:10 119:4 162:23 165:19,22		based 8:25 10:16 20:9 23:20,22,24 30:11 31:19 35:2,4 62:7 75:14 85:2,5 86:14 96:20 98:18 101:11 101:13,15 109:22 123:24 124:24 126:9 128:1,4,6 129:16 133:11,12 134:17 135:1,22 144:5 148:14 155:23 167:8,12 168:22,24 169:11 175:2 176:25 177:4 178:7 179:4 190:23 191:24 192:15	behavior 76:22 81:5 144:10 154:3 192:4
attorney 5:11 220:14			behaviors 154:6
attributable 170:11 200:9			believe 9:6 11:22 19:22 23:5 28:20 31:1 36:15,22 42:4 52:14 53:1 54:9 55:11 60:16 62:19 73:22 74:5,12 86:5 91:22 92:13
attribute 161:9 187:7 201:18			
attribution 162:2			
author 143:14 159:1 160:4			
authors 50:16 88:15 118:9 157:23 160:21 161:9 164:11 165:4 175:12 182:8			

94:21 99:20 100:1 103:1 106:23 112:18 122:17 125:17 136:15 149:15 153:15 154:17 160:7 163:18 170:21 175:21 184:23 187:21 196:4 198:15 209:4 213:3 218:8 believed 160:13,17 189:4 bench 104:12 benefit 16:19 best 7:1 10:2 15:19 18:20 112:19 119:6 125:10,11,19 128:1 220:9 beta 167:18,22,23 better 58:10 140:8,9 beyond 29:16 154:8 bias 163:8 164:10 biases 163:3 big 10:10 83:24 116:21 129:3 binary 170:16 203:7,24 204:18 205:19 bind 41:5 binding 41:5 190:4,12 bindings 192:14 binds 191:22	biochemical 29:5 132:14 135:1,23 143:12,15 144:10 144:12 145:4 163:14 164:2 166:9 171:20 173:18 biochemically 120:20 122:5 144:1 biochemistry 26:8 132:18 134:17 135:6 biological 29:5 biologist 64:6 biology 19:12 20:10,17,22,24 21:2 26:7 64:8,9 98:12 biomechanical 195:7 bird 98:16 bit 10:11 25:12 33:1 64:21,23 77:13 87:8 163:7 black 154:15 blank 111:20 BLAST 97:6,12 110:21 blood 59:19 132:24 blue 127:12 BOARD 1:2 3:2 Bockius 3:16 4:9 bodies 183:21 boil 206:23 207:5 boilerplate	45:10 48:5 104:18 Bolden 2:21 85:25 Boston 4:5 bothered 158:10 bottom 119:12 134:3 bound 204:3,12,17 bounded 204:6 boxed 57:16 138:22 boxes 137:4,8 breached 75:17 breadth 202:9 break 7:12,12,13,16 52:3,6 52:12 89:22,23 131:5,7,13 174:13 174:14 175:3 198:19,21 218:16 218:17 breaks 7:10 218:23 breeding 10:16,22 Brian 1:11 2:2,16,20 3:12 5:2,17,17 13:2 14:22 221:10 222:23 223:23 brief 59:3 bringing 166:4 broad 75:15,21 206:22 broader 39:15 built	115:7,11 bulkier 141:16,18,23 142:11 bunch 16:16 186:4,20,22 192:11 burden 142:22 Burkitt's 18:11,15 business 129:11 144:23 B-R-I-A-N 5:18 B-u-r-k-i-t-t 18:16
C			
C 2:24 13:2 14:22 23:12,14 25:22 32:15 40:13,14,16 40:16,18,25 41:4,5 41:20,20,24,24 45:5 49:13,14,19 54:11 54:11,13,15 55:16 56:6,8,13,18,23 57:13,20,21 58:11 58:17 59:6,6,8,10 59:17,18,23 61:6 62:12,20 63:14,25 73:25 75:20,24 76:13 78:1,10 79:1 79:7,25 81:10 88:12 90:22 91:2,24 92:21 93:1,23,25 96:17,21 97:5 98:18 99:6,10 99:18 100:1,1,5 102:23 105:7 107:10,14 110:9,18 119:10 120:8,8 121:7 122:3 127:16 129:1,3 132:22,23 134:5 137:13 143:7 143:23 144:4,24,24 145:1,5,6,7,8,19,23			

146:1,8,8,13,17 148:6 152:4,6,9 153:7,13 154:15,24 156:4,25,25 158:9 158:10 159:17 161:20 163:24 164:25 165:2,7,13 165:16,23 174:23 176:19,20 179:20 180:9 182:11 184:21 186:9,10,12 186:25 187:6,16,16 187:19 188:7 189:6 189:16 190:5,6 191:11,17 193:5 194:7,11,16 197:8 197:10,10,14,23 198:1,6,10 199:13 199:23 201:10,19 202:12 205:1,4,9,24 206:1,7,8,13,14,15 206:23 207:6,8 208:13,17,22 209:12 213:7,14 214:15,17 215:6,10 216:10,15,21,22 218:13	106:14 109:21 116:7,11,20 119:4 129:11 131:17 151:24 162:16,17 called 18:21 50:10 55:20 57:23 61:8 63:21,21 79:1 88:18,22 92:16 93:4 94:21 107:24 115:23,24 123:12 148:15 159:1 165:8 165:11,12 166:13 209:19 calling 73:16 148:19 152:11 calls 53:19 87:23 113:22 113:23 capable 71:13 capacity 25:15,16 181:19 captioned 221:4 captures 94:24 carbohydrate 145:11 Carcinoscopus 17:17,18 52:21 104:5 110:19 111:13 112:9 114:8 152:4,7 153:5,6,6 157:1,4 163:12 165:15 171:24 172:9 174:22 176:12,20 179:20 197:5,14 198:1	cares 32:21 74:10 carry 46:10 97:18 carrying 119:7 cascade 19:7 23:13,17 67:25 68:1,7,8 69:22,23 69:24 75:20 76:24 81:10 83:22 84:4,5 122:12,14 167:21 175:6 cascades 76:25 81:2 83:12 case 1:6 3:6 6:15 9:11 11:24 12:13 13:2 14:22 17:4 23:15 24:10,16 25:18 27:8 28:12,21 42:19 59:5 67:25 71:1,23 80:3 89:18 101:1 112:1 119:8 128:5 154:9 154:10 156:1 157:19 179:11 216:8,20,21 cases 9:21 10:8 11:8,12 12:5,24 25:17 59:7 72:2 100:25 126:14 173:17 181:15 206:18 210:20 catalytic 121:14 129:10 190:4 190:11 191:13 192:2,6,13 193:4 194:1,2,8 195:6,9 195:18,20 cause 41:6 causes 83:18 caution 8:21 caveat	7:14 134:22 CCP 129:14 cDNA 52:16,19 90:22 97:22 98:3 101:17 102:10 103:12 104:4 106:19 151:5 cDNAs 212:6 Celena 1:19 3:18 4:17 220:4 220:20 cell 18:12 54:15 56:8,9 57:22,24 58:18 59:15,16 60:1,7 73:11,12 cells 20:15,15 55:18 56:7 56:8 57:14,21 58:11 58:18 59:11 60:7,12 62:21 72:11 201:11 201:11 202:13 205:24 206:1,8,13 206:14,16 214:16 218:13 cellular 20:13 21:7 certain 66:7 103:8 108:19 113:8 115:21 150:24 184:15 certainly 27:13 42:11 47:14 68:21 70:15 74:13 88:17 97:1 113:24 115:25 121:10 141:22 144:14 190:22 197:4 206:25 certainty 55:24 103:21 166:24 193:19 certifiable 196:14
---	--	---	--

CERTIFICATE 220:1 Certified 3:19 4:13,14,14,15 4:15,16 220:5 certify 220:6 cetera 123:7 150:4,4 chain 107:1 115:9,10 133:6 134:5 137:20,21,22 138:17 139:5 140:7 140:7,11 148:19 151:11,11,12 193:14,15,15,15,17 chains 141:23 142:1 193:20 challenge 189:2 challenged 44:14 chance 44:23 108:9 change 13:23 15:22 21:1 33:7 68:24 69:1,8 69:10,17 70:1,7,8 72:10,19 73:3 117:11 121:3 122:9 188:10 189:8 204:25 222:2,4,5,7 222:8,10,11,13,14 222:16,17,19,20,22 223:2,4,5,7,8,10,11 223:13,14,16,17,19 223:20,22 changed 37:19 72:9,14,15 117:11 201:25 changes 69:4 75:1 118:5 221:6,7 changing 118:12 characteristic	102:13 204:19 characterization 132:15 143:12,16 145:4 171:21 characterize 19:4 20:19 72:8 82:7 192:19 characterized 18:11,21 101:8 104:25 120:20 122:5 123:19 171:18 190:5,12,19 191:14 192:14,16 192:20,23 characterizes 196:6 charge 113:17,23 114:22 115:1,3,7 charges 114:19 Charles 1:4 3:4 5:12 6:22 9:20 10:6,8,9,14,15 10:17,22,23 16:22 16:24 43:18 107:16 chart 113:7 Chelsea 4:4 5:10 chemical 29:5 chemically 114:21 chemistry 27:4,7,13 Chen 2:14 149:13 152:22 152:25 157:7,17 158:12 159:5,6,14 159:14,18,21,22 Chicago 3:17 4:10 choice 163:1 choose	49:2,6 chop 138:4 CHO-DG44 57:23 59:15 79:3,5 206:14 CHO-GD44 60:12 chromogenic 41:8 175:22 178:6 chymotrypsin 147:21 173:23 174:7 191:21 192:5 194:13 chymotrypsin-med... 145:22 circumstance 115:6 circumstances 76:25 207:1 citations 192:16 cite 64:25 65:25 149:18 150:2 157:3 163:11 168:11 179:14 186:4 cited 65:19 86:5 88:14 131:25 149:12 156:15,17,22 157:17 168:14 181:5 182:4 191:10 195:25 cites 143:17 157:7 159:13 193:20 citing 162:14 185:11 190:10 citrate 54:18 56:19 60:18 61:1,9 63:16 75:25 202:14 203:1,11,14 City 3:17	claim 31:5,10 33:14,18 34:1,18,23 35:10 36:2,3,5,6,6,8,11,12 36:19 37:3,6,7,12 37:14,16,19,21 38:1 38:2,3,4,7,10,12,13 38:13,14,20,25 39:1 39:2,2,3,5,6,8,11,12 39:13,14,15,20,22 40:9,12,15,24 41:15 41:18,22 44:9 48:12 48:13,17,24 49:13 49:23,23 54:1,2,3,7 54:8,9,10,21,25 55:1,8,11,23,23 56:9 60:14,21,22,23 61:4,8,17,19 62:13 63:2,4,21 202:5,9 202:11,15 203:2,5 203:11,12,13,16 204:23 205:8,9,14 206:10 214:18 215:22,25 217:19 claimed 60:15 205:14 213:1 218:1,6 claims 44:13,14 102:2 105:12 188:25 210:11,12 212:13 212:15,25 214:2 217:24 claim's 56:19 clarification 18:14 clarify 43:1 162:4 clean 69:3 clear 32:25 54:9 58:22 73:24 77:25 85:23 89:12 94:11 102:16 113:22 127:14
---	---	---	---

128:18 141:14 179:2 clearly 29:1 77:3 124:8 135:1 140:8 147:16 159:18 163:23 cleavage 138:8 140:15,17,21 140:24 142:12,13 142:19,25 143:4,17 190:3,11 191:12,18 192:12 193:4,10,18 193:19 195:12 cleavages 144:13 cleaved 151:9 193:13 cleaves 83:19 cleaving 41:8 client 6:22 clipped 200:16 clipping 201:25 clone 98:3 103:15,17 197:9 208:16,22 cloned 88:11 208:12 clones 104:17 cloning 119:10 188:7 208:17 close 14:6 151:17 172:5 181:14 183:13 closely 32:16 77:3 172:3 185:20,23,25 209:5 clot 77:2 clotting 23:16 67:25 68:1	75:20 83:22 167:21 cloughran@wolfgr... 4:6 clunky 110:14 Clustal 2:23 111:2,11 116:10 116:12,18,24 117:2 117:8,15,24 118:4,9 118:20 123:1,2 coagulation 19:7 88:12 212:5,18 coding 67:15 92:4,11 94:1,9 94:16 99:5,15 102:22 199:3 212:6 collaboration 14:7 collaboratively 14:1,3 colleague 5:13 collect 197:24 collected 198:3 collection 103:17 collective 32:20 collectively 28:11 colony 10:16 color 67:22 coloring 113:15 color-coded 113:8,12 141:6 column 86:11 159:4 combat 75:18,21 combination 27:21 48:4 53:12	63:17,19,20 combine 35:19 combined 48:6 combining 30:14 come 8:14,19 41:19 52:4 69:19 84:6 85:15,20 112:21 116:17 117:25 120:10 127:3 128:3 130:17 134:12,14 142:15 159:23 178:15 181:10 183:2 comes 82:3 87:3 152:21 167:11 184:12 commercially 174:21 committing 183:3 common 137:21 commonly 131:17 communicate 157:22 communicated 160:16 communication 157:18 159:2,5,14 162:13 communications 157:8,21 companies 9:17 company 10:15 comparable 88:11 155:12 174:21 175:3 176:14,22 178:12,14,21 180:15 181:15 compare	78:25 89:17 126:17 127:24 139:6 146:7 146:10,25 147:5 153:12 155:19 205:18 compared 58:12 75:10 101:19 114:20 125:7 126:23 127:1,4,8,20 129:19 141:24 160:21 164:19 165:1,7 172:18 173:19,25 compares 88:3 126:8 comparing 66:2 124:23 125:14 125:18 126:2 128:1 147:25 153:17 167:5 170:2 171:21 173:11,15 213:4 comparison 23:2 51:16 59:20 87:9,10 110:17,22 113:6 125:14 128:6 128:9,10 153:15 154:9 156:24 160:20 162:12 167:5 172:12 173:5 174:4,4,5 179:19 180:15 185:7 213:13 comparisons 88:5,16 174:2 175:14 183:1 compelling 104:13 compendial 86:14 compensated 14:16 competent 107:12 196:16 complement 125:12 complete
--	---	---	--

40:5 48:3 93:6,15 93:22,25 94:1,1,8,9 94:15,15 96:21 98:21 99:5 110:8 186:12 187:13,13 210:25 211:11,13 211:19 215:10 completed 104:19 completely 103:8 139:2 155:11 155:15 156:11 167:7 187:4 215:1 215:19 216:17,24 complex 18:20 complicated 16:17,17 component 41:12 75:12 122:25 196:14 components 92:7 composition 135:5 154:10 compositions 133:5,12 135:9 136:11 concentrated 198:8 concentration 87:5 146:11,19 147:3 155:17 177:24 198:6 concentrations 64:2 155:15 concept 68:4 80:19 149:20 concepts 23:6 83:24 132:18 Conceptually 51:14 concerned 30:16 42:5 174:9,10 194:8 concise	48:19 concisely 70:6 conclude 73:3 145:6 159:11 166:24 191:25 192:24 concluded 168:6 concluding 178:11 conclusion 116:21 122:8 135:2 147:8 156:12 181:7 181:9 182:13,16 195:21 conclusions 37:18 107:18 116:18 116:20 162:7,8,16 169:5 171:12 172:21 178:11 182:7 190:23 concrete 159:10 conditions 144:25,25 178:15 conduct 30:9 conducting 119:9 confidence 109:4 130:14,19,22 131:1 155:11 confident 109:1,24 110:2 117:6 119:3 129:24 130:24 confirm 15:17 35:13 97:4 108:6 confirmation 124:5,8,9 confirmations 124:4 confirmed 103:22 188:24	confusing 134:13 congratulate 189:22 connectible 47:18 Connecticut 90:15 91:3 95:14 106:13 112:22 connection 6:22 connects 47:15 conservation 111:15,17,19 113:14 114:3 199:18 conservative 113:18 115:17 116:5 116:7 118:19 119:19 conserved 68:10 73:25 78:1 111:16 115:21 116:1,8,14 117:7,18 117:18 119:5 139:12 194:2 195:5 199:5 consider 14:14 19:15 20:6 84:6 109:6,7 115:20 116:17 122:23 135:17 143:6 144:7 consideration 25:11 considered 64:19 100:2 111:21 113:24 115:8 116:1 116:8 123:10 144:2 175:8 181:21 182:3 considering 28:25 143:18 consistent 87:18 89:5 116:4 179:10 187:15 189:15 consistently	164:18 165:6 consisting 54:17 60:25 constant 60:3 constantly 165:6 construe 136:22 208:10 consultant 9:12 consulting 10:23 11:12 contain 52:18,20,25 88:11 94:15 contained 209:8 contains 30:8 52:16,22 59:6 210:8 contaminate 167:24 contaminated 82:18 contaminates 42:6 contaminating 167:20 contamination 84:12 contemplating 52:2 contend 94:19 content 156:8 160:25 contention 190:18 203:17 contents 15:18 context 74:23 122:16 198:12 contiguous 94:2 continuations
--	---	---	--

105:4 continue 46:14,21 continued 74:6 contradictory 215:19 contrary 215:1 control 42:13 51:16 67:22 controlled 85:9 controls 86:15 conversation 9:1 convey 217:24 copy 95:5 131:23 191:7 core 21:1 23:9 corner 108:13 corners 218:3 Corporation 1:7 3:7 8:11 12:14 17:3 correct 6:1,16 8:12,13 11:5,6 11:15 12:9 16:7 20:7,11 21:4,5,11 21:12 22:2 25:5 27:19 28:14 29:21 30:21 32:3,23 33:4 35:5 38:8,10 41:13 44:10,15,16,20 52:21,23 56:25 57:12 58:4 60:8 62:5,24 63:4,5 64:20,24 68:20 73:20 84:16 90:8 91:18 94:13 98:20 101:21,22 103:8	109:12,15,18 113:8 125:17 128:11 132:6,13 133:17,18 134:2 137:3,7,11,15 139:9,10 151:7,20 151:22 158:18 168:20,21 170:14 179:22 184:19,23 185:15,16 186:7,9 186:10 193:14 200:6 202:10 205:5 205:6,10 207:11 corrected 145:11 corrections 221:6 correctly 176:15 correlate 76:4 193:14 correlated 160:24 correlates 76:9,15,23 correlation 183:16 corresponding 117:23 corresponds 101:10 counsel 3:11,11 4:3,8 5:21,22 7:20 8:23 25:3,7 131:2 218:21 219:3 220:11,14 count 114:2,15 133:16,22 133:25 134:12 204:24,25 counted 134:6 counter 186:13 counts 118:11 134:20,23 couple	6:18 25:11 151:24 coupled 31:8 course 11:12 12:11 42:18 43:9 court 4:13 7:11 8:3,6 9:25 16:19 cover 208:2 covered 96:22 151:23 covers 202:12 co-inventors 21:25 crab 17:8,12,13,14,16,18 19:7,8,21 20:3 22:8 22:10,13 23:12,13 24:15,18 43:3,3 46:4,9,12 48:11,14 49:13,15,19 50:10 50:20 51:7,8 54:10 54:12,13 55:15,17 56:24 59:19 64:22 66:6,17 67:21 74:7 75:8,16,18,18,24 76:1,16 77:14 91:16 95:13 97:22 98:4,6 111:12 132:24 crabs 17:6 19:16,24 45:2 64:12,13,15,16,19 65:2,14,18,24 66:2 66:3 67:16 68:2 75:6,9,15 77:5 79:14 89:7,14 122:2 122:5 143:24 158:9 163:25 166:17 171:18 create 104:8,10,11 125:6,9 196:20 created	22:17,19 98:18 101:11,13 creation 22:22 creatures 75:11 criteria 115:19 critical 69:20 CRL 107:16 crosses 68:20 crucial 68:1,3 crystal 123:20 124:3 125:8 125:12 127:25 128:4,7 crystallized 124:6 126:9 130:10 crystallizing 130:6 Cs 74:19 83:12 194:3 CSR 1:19 220:20 CST 5:1 currently 5:19 curve 147:22 cut 105:23 150:14,16 163:7 cysteine 122:23 123:6,7 cysteines 123:5 C's 190:11 C-terminal 148:18 C-terminus
---	--	--	---

148:25 149:1	33:19,19 34:5,7,10	11:17 13:1,6 14:5	definition
C1r	35:16 81:8 91:5	14:10,15,22 15:6,18	26:3 28:6 29:14 33:2
125:12	94:7,21,24 95:1,2	15:22,25 16:6 17:21	33:5,11 48:19 109:8
c9ekeD	96:4,5,9 105:13	25:1,18,21 28:13	109:8 116:7,8 118:7
124:25 125:3,11	109:11,13 117:3	29:22 31:5 33:13,13	203:21
126:15 128:7	130:22 159:9,9	33:21,25 34:12	definitions
D	187:3 188:8 189:23	35:22 36:21,24 37:2	33:9 72:22 73:7
D	195:22,23 196:7,25	37:13,15,24 38:7,10	79:22 118:19
1:19 3:18 4:17 114:7	208:23,24 215:4	38:19 39:8 42:25	204:16 214:10
114:7 220:4,20	218:7 222:23	43:7,10,11,13 49:3	definitive
dairy	223:23	49:8 56:2 57:4,11	19:23
179:25	dated	64:18 65:12 73:19	definitively
damaged	13:12	73:20,23 77:16,22	39:10 148:20
166:9	dates	83:10 86:6 87:12	degenerate
data	34:2 92:14 96:2	88:25 90:24 92:14	107:1
24:6 42:15 50:14,16	Davis	92:15 95:24 97:11	degradation
50:17,23 51:4,6,19	1:19 3:18 4:17 220:4	102:25 106:2	138:3,10 148:13
57:1 58:19,23 61:16	220:20	112:25 124:22	150:22
63:13,23 64:3 70:16	day	132:25 133:1 149:6	degree
77:11 78:12 81:22	118:9 221:8	149:12,23 161:16	27:22,23 103:21,25
82:2 91:2,9 94:18	days	163:11 168:11,14	109:4 111:15
135:17 136:23	110:1,8	174:19 181:6	166:24 192:1,6
139:13,20 143:18	deal	185:12 186:4 196:5	193:19,23 200:12
144:7 147:7,13	172:22	202:3,16 213:17	delivered
154:3 155:1,19	dealt	214:4,10,13 217:8	87:7
156:12 159:15	18:4	217:21 221:2	demonstrate
160:12 162:12,24	decades	declarations	182:10
163:6 167:12 170:1	81:2 118:4	12:8,24 24:22 26:19	demonstrated
170:25 171:10,12	December	42:19 44:1 86:19	78:9
173:23 177:1	13:12 15:9,13 31:6	90:5 131:16	demonstrates
180:14,24 181:1,12	32:3 33:14 34:3,5,9	declare	191:10
182:10,19,25	34:9 73:24 77:25	221:3	depend
190:21 195:16	90:20 91:24 94:7	deemed	31:19
210:8,9,9 213:10,22	105:14 109:14	34:10	dependent
213:22	174:24 188:11	deficiencies	33:10 107:5 137:18
database	208:25	35:3,4	142:18 172:23
24:12,13 91:10 99:21	decide	define	depending
100:11 102:4	101:6	72:17,24 86:24	33:8 60:5 72:24
123:25,25 125:8,9	decided	defined	150:19 175:19
129:6,8,9,17,25	118:10 170:6	25:1 76:9,14 79:24	180:11 198:6
130:10,12,24	decimals	80:6 108:11 203:7	depends
databases	134:23	214:18 217:8	115:5 180:10 192:18
45:9	decision	defining	deposit
date	203:8 205:20	74:4	97:1,2
9:7 15:9 31:7 33:15	declaration	definitely	deposited
	2:16,20 11:3,14,16	209:8	24:6 90:14 91:3,10

94:18 95:13 109:9 deposition 1:11 2:2 3:12 5:1 6:10,11,14 7:11 11:21 12:8 16:18 106:13 110:3 220:7 220:12 221:1,4,6 222:1 223:1 depositions 3:15 deposits 24:15,18 53:13 91:15 99:16 112:22 depth 100:3 derive 158:10 derived 106:20 152:7,9 157:20 158:3 159:16 215:11 describe 46:1 59:2,14 60:9 79:20 90:6 97:19 106:9 109:22 110:1 111:9 196:5 217:3,3 217:4,17 described 45:22 46:3 48:22,23 58:6 87:18,20 101:8 104:15 121:24 150:11 155:24 206:5 211:20 212:11 213:4 describes 50:2 56:7 describing 46:17 58:10 79:19 description 31:9,18 41:23 44:9 44:13 58:13 163:12 197:4 214:7,21 217:2,13,18,22 descriptions 25:14 197:25 210:12 210:19	design 88:10 103:7 106:25 147:2 designations 115:14 designators 125:5 designed 123:6 detail 36:8 106:4 213:20,23 detailed 30:8 details 56:17 77:4 detect 23:17 74:19,21 76:13 122:12,14 177:2,7 196:21,24 detected 60:11 167:18 177:18 detecting 40:18 detection 22:18,19,20,24,25 40:25 74:11,16 75:6 122:15 180:5 196:11,16 197:2,6 213:5 detergent 153:8,14 154:16,18 154:19,21 155:15 156:9,10 158:23 detergents 153:2 154:4,11,17 determine 18:7 97:8 183:21 215:14 determined 125:19,21 126:3 139:6,7 determining 28:2 113:18 136:4 148:14 developing 29:6	deviations 142:2 device 179:12 devices 42:6 184:4 diagram 148:5 dialyzed 198:8 diet 215:11 differ 103:25 136:6 difference 69:11 114:22 115:1,4 122:6 140:20 141:14 144:9 147:9 156:7 165:22 166:22 169:1 170:1 170:7,10 180:21 181:4,11 183:6,9 185:3 197:21 200:8 200:22,23 201:2,2 201:18,19 214:7 216:4,19 217:1 differences 69:12 70:13,14 79:10 113:11,17,24 114:18 116:16,23 127:10,12 134:20 135:13 136:9 141:4 144:15 147:2 154:2 160:23 161:10,19 167:14,16 168:4 172:23 175:17,19 180:5,19 181:2,3,17 181:18,20 182:2,20 185:13,17 different 18:22 20:21 23:3 37:11,18 38:1,3,21 39:5 55:22 60:5 64:14 67:20 74:7 76:20 77:18 78:10 81:3 82:14 83:3	85:3,15 88:6 89:6,7 89:14 100:22 114:19 115:14 117:25 118:3,13,20 121:20 128:16 129:4 130:11,13,18 130:23 131:1 134:9 134:10 135:10 136:12 138:13 139:16 146:2,19,24 149:5 152:16 153:19,21 154:7,17 155:11,15 156:11 159:7,8 161:21 165:1,2,23,25 166:5 166:15 167:1,7,10 169:23,25 170:9 172:24 173:1 176:12,20 177:13 178:2,17 180:16 182:22 186:5,18,20 194:7 200:4,17 201:10 203:20 204:5,15,16,21 205:16,17,17 215:2 216:7,18 218:9 differential 85:3 differently 120:21 differing 162:2,3 differs 201:6 difficult 155:18 180:24 186:14,16 187:18 188:6,13 208:12,12 208:20 difficulties 107:20 difficulty 51:17 209:11 direct 21:24 81:22 193:3 directed
---	--	--	---

179:8	202:4 208:23,25	14:1 15:3,8 40:1,4	159:14,18,21,22
direction	discussion	43:23 65:3,9 66:15	169:19 174:16
220:10	8:23 39:4 66:13	85:24 95:6 111:6,7	186:13 188:2,12
directions	71:10 132:9 160:20	111:9,10 124:18	189:4 196:9 198:23
50:7 179:9,10	161:7 162:6,6,15,18	149:5,5 156:21	202:8 205:22 207:9
directly	162:19,25 163:2,16	168:12 207:23	208:7 209:7 214:13
21:16 64:12,14	163:20 164:3,6,8,12	208:3 209:2,4,5,7	214:20 215:1,12
105:20 191:17	166:11 175:2	210:4,8,14 213:20	216:5 218:19,25
193:25 198:7	disincentive	218:3	draft
disagree	159:25	documents	106:14 109:20
35:6 67:13 92:16	dispute	16:4,9 33:6 123:13	draw
136:21 202:8 211:5	67:7	213:19	80:16 135:2 147:8
disagreed	distinct	doing	162:8 178:6,10
208:14	72:6 121:24 146:21	53:21 80:14 85:8	181:6 195:21
disagreement	177:25 178:1	123:16 138:10	drawing
152:18	distinction	domain	165:18,21 172:21
disciplines	127:21 140:11	69:17 119:14,23,25	181:8 182:21
20:21	182:21 199:13	120:1,3,4 121:6,12	dream
disclose	distinguishable	121:17,20 124:11	207:1
160:2	74:22 191:23	129:10,11 141:12	Drive
disclosed	diverged	142:12	3:17 4:10
106:23 152:2 187:14	66:25	domains	dry
disclosure	divergence	68:15,17,20 70:22,25	163:7
31:7 93:4 94:10	65:13,20,21 66:8,10	113:12 121:3 129:4	due
112:19 116:4,6	66:20 67:1,11,17	129:6,14 141:3	168:5 201:3
125:16 215:7	68:18,22,22 139:21	194:8	duly
217:23	divergent	dot	5:3 220:8
disclosures	66:21 117:13	111:18	duplicate
93:6,15	diverging	dots	2:20
Discovery	66:16	111:17 115:3 180:23	dust
3:13	diverse	181:14	156:18
discuss	194:3	double-dot	
16:11,12,14 24:6	divorce	114:3,15,16	E
35:22 52:11 90:2	6:12	doubt	earlier
131:12 132:11	divulge	117:10	33:18 53:25 77:13
discussed	8:22 157:21	Dr	78:15 90:18 91:22
43:7 54:2 132:19	DNA	5:7 8:10,22 11:5,8,9	93:5,14,22 94:12,14
144:21 149:23	98:14	11:11,13,18,24 12:1	104:2 105:4 118:15
154:1 209:7	doable	12:4,11 13:4 15:1	121:2 153:20 207:9
discusses	104:22 110:15	16:15 22:3 26:19,23	early
66:10 115:17 132:21	Doctor	26:25 28:13,16,24	118:11 143:11
discussing	24:20 43:23 56:2	34:6 35:4,6 36:1	173:17
35:12 58:20 74:25	63:11 65:9 102:24	52:8 64:5 71:19	easier
123:14 132:14	157:25 192:9	89:25 107:16,22,24	108:21 146:24
144:22 156:2,3	document	109:8 123:14 131:9	easily
169:20 172:17	13:5,11,15,22,25	144:9 157:17	45:9,20 46:13,25

53:12 92:7 103:3 215:10 EBNA1 18:8 19:2 edited 14:6 editing 25:13 education 28:10,18,25 29:4 educational 26:14 effect 142:23 effective 218:6 efficiency 143:1 efficient 30:15 efficiently 147:22 either 32:23 46:12 59:18 60:16 79:3 92:10,16 93:18,25 96:19 99:21 112:12 132:8 165:19 166:3 182:14 183:24 187:5 201:2 203:8 203:25 204:7 206:16 elicited 71:24 elucidate 71:2 Embryonic 54:14 emphasize 135:16 emphasized 127:11 employed 220:11,14 employee 9:12 220:13	enable 171:6 enablement 31:10,18 44:9,13 202:5 214:8,21 217:2 enables 171:11 encompassed 203:23 encounter 32:19 ended 31:2 endotoxin 22:17,19,20,24,25 23:3,17 40:18 41:1 41:13,16,19 42:3,5 42:10,12 74:11,16 74:20,21 75:6,14 76:13 82:18 89:8,9 120:22 122:13,15 122:15,20 160:25 164:19 165:1,7 174:23 175:10 176:5 177:3,8,14,18 177:21 178:25 179:1,3,4 180:5 196:11,14,17,21,24 197:2,5 198:11,12 213:4 endpoints 203:22,23 ends 8:16,18 30:17 101:4 107:3,3 129:2 134:16 138:6,8 204:6 engineering 29:5 enhanced 153:7,13 enhancement 154:24 155:4 entails 179:8	enter 75:17 entire 28:10 47:23 92:3,3 92:10 129:15 151:6 159:20 172:25 221:4 entirely 30:10 166:7 entirety 91:16 196:4 entities 85:11 143:25 156:11 164:1 entitled 31:6 33:14 entity 9:12 enzymatic 77:18 145:18 147:9 enzyme 85:16 98:23,25 99:7 99:11 100:12 101:10 110:18 121:15 132:16 136:5 146:10 158:11 170:4,5 178:24 192:4 199:3 enzymes 23:24 68:2 76:5,10 76:22 80:23 83:13 122:7 142:20,24 143:20 144:5,10 147:21 171:17 172:25 174:6 178:19 192:21,22 192:25 193:24 197:4 Epstein-Barr 18:5,8,17,19,22 20:14 21:22 EP670 107:17 equally 50:8 99:24 188:11 equates	180:21 equivalent 81:5 98:1 99:8 100:2 100:10 101:18 102:23 142:21,24 143:1,1,20 144:2,14 182:1 183:23 184:6 184:7,9 ERRATA 221:1,7 222:1 223:1 error 61:15 62:18 82:4 136:1 145:9 180:23 escape 72:3,10 essential 75:21 essentially 84:23 120:10 132:24 164:7 195:10 207:12 established 174:21 187:2,6 establishes 160:13 estimate 123:18,22 134:16 136:20 estimated 136:18 estimates 160:21,22,24 161:7 164:19 165:1,7 182:11 et 2:14 65:1 86:1 123:7 150:4,4 179:15 Europe 74:16 81:4 82:12 European 188:2,23 189:3,11,22 209:7 evaluate 180:25 212:14 evaluated 22:24
--	--	---	--

event 142:25	73:18,19 75:16 84:2 88:3,5 113:25 121:13 133:13,19 138:16 140:25 149:25 154:14 155:16 160:1 175:4 175:14,21 176:3 177:10 200:4 201:9 206:23 213:13 214:3	129:20 130:11 212:19	explicitly 45:1,25 88:19
events 142:19 144:12		existing 129:16,18 130:9	exposure 24:11 182:12
eventually 183:9		exists 36:10 91:9	express 197:15
everybody 7:12 152:21		exon-exon 102:12	expressed 51:19 54:14 55:18 58:17 59:23,24 101:3 102:8 200:18 200:22
evidence 100:25 120:13 121:24 142:23 150:3	examples 47:25 50:9,19,19	expect 53:16 66:3 82:12 107:19 120:17 144:11 153:20 185:23 208:19,20	expressing 60:6
EVNAs 18:22	exceedingly 155:18 170:5	expectation 107:14 128:15 154:6	expression 56:6,13 60:8
evolution 74:25	Excellent 22:16	expected 144:4 193:15 214:14	extensive 37:8 64:9 106:24 143:12,15 171:20
evolutionary 64:21 65:1 66:8 68:3 186:1	exceptions 181:24 200:18	experience 26:8 27:14,18,22,23 29:4,12,13 30:11,12 81:7	extensively 27:2 74:8 122:5
evolve 66:4 72:2	exclude 28:9	experiences 29:19	extrapolate 154:3
exact 37:8 59:1 61:3 66:12 92:14 117:5 134:12 134:14,23 135:22 136:4 143:21 151:25 174:3 184:23 190:21 214:9	exhibit 2:6,7,8,9,10,11,12,13 2:14,15,16,17,18,19 2:20,20,21,22,23 13:1,5,8 14:20,21 14:24 15:2,2 39:24 40:2 43:17,18,21 65:4,5,7 70:18,19 71:9 85:25 86:2 95:4,8 110:24 111:1 111:3 113:1,10,16 113:20 116:3 118:1 124:14,15 131:20 131:25 149:7,8,11 150:2 152:3,6 156:16 164:14 168:7,11 175:5 176:21 179:14,15 179:16 190:9,16,25 191:3,6 207:18,21	experimental 30:19 147:2	extrapolating 172:22
exactly 31:22 35:11 77:9 82:1,1 83:16 84:20 87:24 92:1 107:18 110:23 117:17 146:4 183:2 184:25 185:6,20,21,23 195:8 215:15		experiments 42:14,18,23 43:6,9 43:12 155:12,16,19 155:23 156:9	extremely 37:7 108:14 182:14 184:2 194:5
examination 5:5 174:9		expert 11:23 19:17 22:12 23:10 64:17 80:2	F
EXAMINERS 2:1	Exhibiting 60:23	expertise 9:1 19:10,24 20:4	face 96:5 160:11 210:9
example 6:15 34:13 46:5 55:3 56:6,12,12,14,16,23 56:25 61:20 65:11 66:15 67:21 68:23	exhibits 2:5,25 54:16 103:2 190:13 191:3	experts 11:1	facilities 180:11 182:12
	existed	explain 136:9	facility 180:5
		explains 205:23	fact 15:12 16:8 21:1 22:10 26:22 28:8 32:15 35:14,24 58:2 64:25 70:12 76:25 96:8 114:18 120:19 130:14 146:9 147:20 148:1 171:17 172:24 183:19 187:12,15 189:11 192:16
		explanation 25:7 53:4 206:2,3	
		explicit 45:6	

200:6	191:17 193:5 194:3	far	218:6
Factor	194:7,11,16 197:8,9	47:20 117:18 137:17	fill
2:24 23:12,14 32:15	197:10,14,23 198:1	153:24 168:24	96:23 97:3,20,22
40:13,14,16,16,18	198:6,10 199:13,23	171:13 180:25	98:2 106:5
40:25 41:4,5,20,20	201:10,19 202:12	181:24 195:17	filled
41:24,24 45:5 49:13	205:1,4,9,24 206:1	209:19 211:14	106:15
49:14,19 54:11,11	206:7,8,13,14,15,23	farms	filled-in
54:13,15 55:16 56:6	207:6,8 208:13,17	179:25	142:1
56:8,13,18,23 57:13	208:22 209:12	favor	filling
57:20,21 58:11,17	213:7,14 214:15,17	110:14	31:19,23
59:6,6,8,10,17,18	215:6,10 216:10,15	feature	final
59:23 61:6 62:12,20	216:21,22 218:13	75:7 123:25 206:4	103:6 127:4 135:21
63:14,25 73:25	factors	features	139:7
74:19 75:20,24	68:12 85:15 98:22	60:10 126:8	Finally
76:13 78:1,10 79:1	137:18 147:3	February	17:16
79:7,25 81:10 83:12	facts	1:13 3:15	financially
88:12 90:22 91:2,24	162:13 188:17	feel	220:15
92:21 93:1,23,25	209:18 210:21	76:19	find
96:17,21 97:5 98:18	fair	field	48:3 116:23 117:4
98:25 99:6,6,10,10	27:16 28:3 37:1	19:8,9 27:14 28:7	124:12 143:21
99:18 100:1,1,5,14	46:19 53:7 58:9,13	29:8 157:21 158:4,8	165:9 183:9 202:18
100:15 102:23	62:17 66:24 91:3	179:24 186:19	finding
105:7 107:10,14	165:21 170:23	196:9,10,13,19	47:10
110:9,18 119:10	176:6,22 200:21	Fifty-six	findings
120:8,8 121:7 122:3	207:13	56:3	50:7 191:13,24
127:16 129:1,3	fairly	figure	finds
132:22,23 134:5	16:17 79:21 104:19	57:7,10 58:1 61:5,16	128:1
137:13 143:7,23	116:7 130:24	61:21 63:18 77:13	finer
144:4,24,24 145:1,5	139:22 143:12	78:14 84:3 97:11	77:4
145:6,7,8,19,23	150:16 211:10	119:11 137:2	finish
146:1,8,8,13,17	218:8	139:13 145:10,20	83:7 162:1 169:19
148:6 152:4,6,9	faith	145:23 146:4	219:4
153:7,13 154:15,24	153:24	153:19,19 154:14	finished
156:4,25,25 158:9	fall	154:20,22,23	9:24
158:10 159:17	203:1 205:4,9	155:16 174:1	firm
161:19 163:24	falling	175:15 176:3,8,13	5:11,14
164:25 165:2,7,13	214:17	177:24 180:4,25	first
165:16,23 167:19	falls	193:9	12:25 23:23,23 26:18
167:20 168:2,5	205:11 206:8	figures	51:18 86:11 92:10
174:23 176:19,20	false	66:15 103:3 155:11	92:25 93:3 112:6
179:20 180:9	167:25,25	156:6 174:3 210:18	140:13 143:14
182:11 184:21	familiar	217:24	148:22 158:24
186:9,10,12,25	9:18,22 10:11 11:10	filed	163:6 177:12 178:3
187:5,15,16,18	21:8 23:5,18 26:22	43:19 44:4,8,12,22	197:9 208:1
188:7 189:6,16	28:17,18 30:2 51:14	93:9 104:3	fit
190:5,6,11 191:11	98:7 119:3 122:16	filing	125:10,11,19 128:1

flag 112:2	170:13 171:9,18 172:14 176:24	28:13 107:16,22,24 188:2 189:4 208:7 209:7	77:17 78:1 79:14 80:16 81:5 82:10,17 82:22 83:1,2,8,11 84:1,4,7 120:5 144:14 171:25 172:4,10 178:12,14 185:9 192:23
flagged 111:24	177:22 182:6,24 187:20 191:15	Frohman's 28:16,24 188:12	functioning 122:15
flexibility 108:25	192:17 193:6 197:23 198:2	front 15:1 37:22 44:18,22 47:4,5 71:9 95:16 128:22 132:2 175:6	functions 67:20 72:13,14 73:9 83:21,23 142:20
Flora 4:4 5:14	200:10 204:4 205:15 206:20	full 31:10,25 32:2,4,4,12 45:8 48:8 92:8 94:3 97:5 99:13,14 106:15 107:9,14 109:22 113:13 124:4 146:21 151:5 159:17 215:5 217:4 217:19	fungi 167:23
flow 21:13	207:14 209:6 210:2 211:7,21 217:6,20	fully 111:16 211:21 215:5	further 30:12 56:5 67:19 127:11 152:1 220:13
fluo@wolfgreenfie... 4:6	formal 23:2	full-length 138:4 212:4,17	furthermore 103:5 115:13
focus 18:2 135:18 140:6 147:20 163:6	formed 35:24 38:9	function 69:1,6,18 70:8,9,14 71:3,17 72:9,10,18 72:25 73:1,8,13,16 73:16,17 75:1 77:15 77:18 78:19 79:13 80:3,16 117:23 121:4 129:13 143:9 174:21 175:4 176:14,22 191:17 194:17 195:17 199:18 211:1	G
focused 34:4,6 35:15 67:17 68:23 101:7 144:3 153:2	forming 12:12 42:18,24	functional 68:15,16 69:10,12,17 70:1,21,24 99:24 113:12 119:23 120:1,18,25 121:3,6 121:12,17,20,21 122:6,10,11,18 129:4,6 141:3 143:20 150:19 181:19 199:3	g 167:19,20 168:2,5
follow 181:14	forms 79:2,3,5,5 101:2	functionally 73:25 74:3,14,17,22	gap 96:21,24 97:3,16,17 97:20,22
followed 208:22	Forn 179:15		gaps 31:19,23 106:6
following 97:3 179:9	forward 103:19		gather 106:14 117:21 197:16 198:19
follows 5:4	fossils 64:19		gathered 48:7
follow-up 84:24 104:15	found 35:4 36:3 47:17 129:9 145:7 167:15		gears 89:21
follow-ups 82:20	foundation 19:12 20:12 213:8		gene 100:21 114:21 186:18
foregoing 220:7	four 74:1 100:14,15 112:5 140:13 177:14 218:3		general 70:6 173:8 188:1 196:15
form 18:24 33:17 35:14,18 37:4 40:19 41:2 49:22 53:8 55:10 58:15 60:2 73:5 77:20 79:15 83:4 86:23 87:19 89:3 93:2 94:16 100:17 100:24 105:2,9 106:8 135:12 136:13 147:10 157:13 161:12 162:22 169:14	frame 24:3,3 101:9 209:9 215:8		generally 75:7 79:6 83:20 88:9 116:18
	frames 215:3 216:20		generate
	frankly 81:23		
	fraud 183:4		
	free 7:4 150:17,23 151:12 163:8 164:10		
	Frohman		

48:8 138:6 214:15 generation 65:18 generically 46:5 genes 211:1 genetically 172:5 genetics 69:14 genome 67:12,14 91:16,19 genomes 67:16 Genomic 2:12 genous 210:24 geographically 66:22 gestalt 115:6 getting 30:16 129:2 give 6:6 7:11 46:15 47:7 48:19 51:3 83:16 84:10,11 89:9 100:20 107:9 115:2 126:11 137:16 140:5 143:21 146:3 150:17 151:5,7,9,16 152:13 167:19,24 171:14 178:20 182:7 183:24 192:5 207:7 given 32:15 39:24 43:11,21 46:9,11 65:7 66:22 69:15 108:24 117:17 130:14 135:18 142:17 147:22 170:8 180:15 187:8 192:3 194:7 201:15	gives 103:20 124:7 205:25 giving 25:14 46:5,21 151:17 182:19 global 178:6,10 glucans 167:18,22,24 glycine 140:1 glycoprotein 73:9,10 glycosylation 139:1,11,17 go 38:24 52:4 94:2 104:15,20 112:5 131:6 137:17 146:13 198:25 goal 18:6,25 70:20 100:8 100:9 122:19 goes 130:16 152:20 180:10 going 6:18,20,25 7:6 8:6 14:20 16:18,20 20:1 23:11 24:5 31:3 40:1 43:16 46:14 49:8 51:25 66:19 68:22,25 69:2,5,5 69:25 70:18 77:7,14 78:23 82:12,15,16 83:4,16 84:18,21 87:3 89:21 101:6 109:3 116:15,16 119:6 121:15,18,21 122:9,18 124:13 131:2,23 135:20,25 146:3 147:24 149:4 149:20 152:13 162:15,23 163:5 178:23,25 179:3 183:5,9,15,19	185:10,24 203:5 213:25 good 5:7,9,10 52:9,10 90:1 90:2 96:22 101:25 118:5 124:7 131:9 136:3 139:4,5 174:17 198:24 210:10 gotten 91:1 166:15 167:1 169:25 215:21 216:9 grain 139:20 grand 66:4 granted 17:24 27:18 granularity 116:12 graph 78:15 147:18 180:4,6 graphical 97:14 113:9 grasp 118:5 great 8:9 40:7 66:2 108:24 132:20 153:3 172:22 181:14 196:23 greater 61:11 62:4,23 151:1 151:15,18 158:15 160:12,14 169:9 203:4,10,25 204:1,7 greater-than-90-pe... 160:9 green 112:1,8 Greenfield 4:3 5:11 ground 6:18 group	54:17 60:25 187:17 groups 111:17,19 114:4 115:21 guaranteed 107:9 108:7 guess 52:5 62:25 79:9 80:22 148:7 154:5 154:23 158:7 191:8 199:20 217:15 guesstimation 62:7 guidelines 84:25 87:16 89:13,15 H hand 12:25 14:20 40:1 43:16 65:3 85:24 95:5 110:24 124:13 131:23 149:4 190:25 handed 13:4 207:21 happen 108:14 198:9 happening 147:23 happens 112:6 206:6 happy 33:22 hard 127:10 146:7 147:5 180:25 hard-pressed 37:17 harmonization 89:15 harmonized 86:15 89:1 harmonizing 173:14 harvested 166:17
--	--	--	--

head 62:1 99:14 141:8 166:20 185:1 217:9	183:8 184:7 186:1 192:1,5 193:19,23 210:14	24:15,18 43:3,3 45:2 46:4,9 48:11 49:13,15,19 51:8 54:10,12,13 55:15 55:17 64:11,13,15 64:16,19,22 65:2,13 65:18 66:2,3 75:6,8 75:9,24 76:1,16 77:13 79:13 91:16 95:13 97:22 98:4,6 143:24 158:9	170:6 183:15 190:10
heading 25:22	higher 54:17,19 57:14,20 59:11,17 60:17,19 60:25 61:1 62:9 63:3 79:4,6 123:2 160:21 161:7 164:18 165:1,6 176:5 177:21 180:9 202:22,22 203:13 203:15,18 205:12 205:25 206:15	host 56:8,9 72:11,12 73:11,12,14 106:4 200:16	identical 38:4 39:12 44:18 74:1,3,18 77:17 78:2,20 79:14 80:17 81:20,21 82:3,5,12 82:15,22,25 83:1,2 83:9,11,23 84:1,4,7 84:15,19,21 86:13 87:2 116:20 138:20 139:11 143:24 144:4 147:13 152:8 164:1 171:1,15 172:1 175:13 183:12,14 192:25 199:16
headwinds 32:19	highest 125:23 180:20	hour 7:11 14:19 52:1	identification 21:23 158:20 210:25 211:12
heard 9:14,19 11:7 23:14 51:19	highly 69:24 73:25 78:1 80:24 151:16 158:8 173:21 194:2 199:5	hourly 14:16	identified 92:13 144:15
heavy 107:1 137:20 140:7 148:19 151:10 193:15,17	high-scoring 129:23	house 156:18	identify 18:25 19:1 21:7 70:21,24 90:22 100:21 101:17 138:21 149:2 151:15,21
height 62:8	Hikaru 208:3	huge 118:25 169:2	identity 68:19 84:22 151:2 171:17 185:2,5,8,18 186:1
HEK 54:15 56:8 62:16,16 62:21 63:25 202:12 205:2,2 206:8,12,13 218:13	history 64:22 65:2	human 18:17 54:14 55:18	III 18:21
HEK293 55:18 57:23 59:15 60:12 61:6,10,14,22 79:3,6 214:16	hold 133:2 163:22 189:23	humans 183:12	IL 4:14
helix 142:6	holding 60:3	hundred 67:9	Illinois 3:18,20 4:10 220:6
Hello 52:8 89:25 174:16 198:23 218:20	home 181:12	hydrophilicity 115:9	imagine 62:1 95:2 117:15
helpful 48:20 141:9	homologous 170:19	hydrophobic 139:25 140:2	immaterial 164:4
helping 14:9	homology 152:5 157:4 158:16 160:8,9,13 161:16 168:15,16 169:13 170:11,15,15 192:3 192:22 193:23	Hydrophobicity 115:8	immune 20:16 72:4,15 75:11 75:13
hemocytes 143:23 163:25	hopefully 8:2	hydrophyllic 140:3	immunological
hereof 221:7	horseshoe 17:6,12,13,16 19:7,8 19:16,21,23 20:3 22:8,9,13 23:12,13	hypothetical 207:4 212:22	
hesitant 162:8 178:6		I	
hey 116:22 168:4 174:6		icing 172:2	
Hi 218:19		idea 69:19 79:12 124:7 166:13 167:18	
high 107:13 109:4 139:21			

132:15 163:13 immunologically 143:25 164:2 immunology 17:24 20:9,12,13,17 20:22,23,25 28:20 impact 69:1 71:17 72:19 73:2,3 120:13 121:4 121:11,18,22 122:10,11,18 142:13 143:3 167:11 impactful 171:11 impacts 71:12 75:8 impediment 19:16 implication 140:20 implied 208:11 imply 186:11 important 67:24 70:9 71:3,4,5 105:11 129:13 153:16 171:13 184:2 impossible 84:23 impressively 178:2 improbable 194:5 incentive 32:17 159:24 include 30:19 45:4,6 49:18 50:17 53:5 61:15 62:18 70:16 97:10 120:24 177:2 193:3 201:24 included 42:8 47:11 50:11,17	50:18 63:15 67:16 85:18 103:2 105:7 113:14 118:1 120:7 214:10 includes 37:2 56:6,16 64:1 105:20 146:9 193:7 including 20:21 31:1 51:7 56:19 85:16 88:19 143:13 144:13 162:13 192:12 217:23 incomplete 212:22 incorrect 34:10 139:8 207:13 incubate 150:13 incubation 110:12 146:21 independent 103:14 107:4 independently 126:16 INDEX 2:1 indicate 143:22 151:14 163:24 indicated 12:7 17:23 99:20 148:23 151:14 169:11,21 207:12 221:6 indicating 111:16,17,18 indication 113:13 186:16 indications 187:11 indirectly 21:19 indistinguishable 120:11 133:7 163:13 172:4 191:19	individual 11:4 133:4 135:4 individually 74:7 individuals 14:9 71:24 75:2 industrial 29:6 industry 74:10,15 infect 72:11 infection 75:18 infections 18:17 inferior 166:9 influence 128:2 inform 43:6,10,10 65:22 information 32:10 45:2,21,21 46:11,22 47:1,6,15 47:18 48:3,4,10 52:17,21,22,25 53:2 53:6,17 59:22,24 63:23 65:23,25 66:1 76:8 77:8 90:6 93:11 94:6 95:25 96:13 98:2,3 103:20 109:25 117:22 124:10 143:5 150:13 151:8 152:3 157:16 193:3 194:1 195:1,20 197:8 198:17 212:17 informative 193:9 informed 23:6 25:3 infringe 48:24 infringement 49:1,10	inherent 136:1 inherently 162:7,17 inhibited 153:7,13 inhibition 56:16 132:13 inhibitors 59:7 153:25 initial 25:14 104:14 injected 184:3 Injection 56:17 innate 75:13 input 126:6 127:23 inquiry 218:2 insect 58:18 59:18 60:7,13 201:11 206:1,16 inside 75:17 insights 71:3 inspect 55:23 inspection 141:13 142:7 instance 183:16 instances 181:16,18 instructions 119:7,8 instructs 7:20 intact 150:18 integrity 71:6 intended
---	---	---	--

160:1 intensely 100:22 intent 30:23 intention 136:22 intentionally 71:1 interact 68:9,10 69:22 interacting 71:13 interaction 11:18 interactions 10:7 12:16,19 71:5 123:3 199:4 interchangeability 85:1 86:14,20,21 87:17 88:24 89:4 interchangeable 74:14 82:11 87:13 171:25 172:10 interested 159:18 220:15 internal 193:16 international 86:16 89:2,16 179:5 184:10 internationally 89:19 interpose 8:21 155:6 interpret 192:18,20 211:9,17 interpretation 61:18 162:11 interpreted 40:20 intervals 130:19 intrinsically 204:21 introduce	12:23 170:6 introduced 86:2 95:8 111:3 124:15 131:20 149:8 168:7 179:16 191:4 199:14 207:18 invade 73:12 invariant 195:10 invented 44:23 58:14 105:6 189:16,17 218:1 invention 21:20,21 45:8,22 46:11 50:8,11 58:7 60:10 105:1 212:4 212:10,14,20,24 217:3,5,17 inventiveness 188:24 inventor 26:6,11,13,19 149:13 158:12 207:10 218:1,5 inventors 12:17,20 19:14 26:2 26:12,15,17 31:13 31:15 44:22 45:7,11 45:15,23,25 46:3,9 46:16 50:2,5 53:6 53:16,20,21 55:20 58:6,9,16 59:9 60:4 61:22 63:12 78:9 90:21 93:9,9 104:3 104:24 105:3,10,11 112:19 116:4,6,19 118:18 119:4 125:16 149:19 150:25 153:4 188:20 189:5,16,22 200:7 201:8 208:4,8 208:10 209:1,11,16 209:17 210:23 211:10 212:20	213:3 215:7 inventor's 153:18 211:6 investigate 145:15 investigator 19:9 107:12 157:20 158:3 investigators 74:9 81:25 84:20 involve 19:6 involved 8:14,19 10:8 11:1,8 12:2,5,20 22:22 23:6,15 24:10 212:5 212:18 involving 75:20 ion 58:24 75:24 76:15 77:4 79:25 132:13 ionic 77:6 154:10 ions 59:7 64:1 156:10 IPR 8:15,16,19 13:5 15:24 17:21 25:21 33:4,12 40:3 43:18 56:2 65:4 73:20 85:25 90:10,11,23 91:6 131:25 149:11 156:17 202:3 219:1 IPR2025-00440 1:6 3:6 13:3 irrelevant 102:2 irrespective 69:14 isoelectric 122:23 isolated 143:23 163:24 isoleucine 148:8,22,23	issue 49:1 73:15 issues 23:9 items 55:21 Iwanaga 2:10 J Jain 11:24 12:1,4 123:14 214:13 215:1,12 Jain's 35:4,6 109:8 186:13 202:8 214:20 216:5 Japan 74:16 81:4 82:11 85:8 209:6 Japanese 9:17 17:12 143:24 163:25 joined 8:2 journal 32:6,8,18 judge 212:24 judges 192:11 junction 102:13 K Karen 92:18 Kawabata 26:7 keep 183:19 key 68:14,16 70:21 72:13 75:12 113:10 147:1 199:2 Kidney 54:15
---	---	---	--

kill 121:15	123:21 124:3 126:5 128:1 129:11,22,25 130:14 131:18 135:5,14 136:5 140:4 141:7 142:17 142:17,20 143:10 143:18 145:9 147:3 147:24 148:16,20 148:22,25 150:14 151:7,17 153:24 154:7 155:10 157:14 158:19 162:12 163:1,4,16 166:1,2,7 167:9,12 167:19 168:25 169:22 171:24 172:1,9,23 173:6 175:12 177:4,5,5 178:17,22 179:11 180:20,24 181:13 181:19 183:7,9,11 184:1,16 185:19 188:14,15 190:13 191:18,20,22 192:2 193:12,19,21 198:6 200:13 204:7 205:19 206:6,21 209:4,6,16,16 211:9 211:11,16 215:4,9 216:14,17,21	197:15 198:13,14 216:10	lanes 176:4
killed 75:19		knows 134:22	language 25:13 36:7,11 37:8 37:16 38:16 41:4 54:9 55:4,4,8,9,13 79:21 185:4
kind 25:15 51:19 77:7 83:23 85:21 122:18 150:21 151:8 207:7		KS 4:14	
kinds 71:6 84:10 104:16 153:1		L	large 18:19 43:17 120:3 129:22
kinetic 173:23		L 148:15 193:15	larger 137:13 160:23,24
kit 23:18 85:17,19 196:15		lab 10:13 20:19 22:4,6,8 22:10,18,20 23:1 30:5 42:17 43:8,12	late 24:4,4
kits 22:20,24,25 23:3,25 88:5 198:15,16		labeled 154:22	latency 18:5,11,20,21,24,25
knew 143:17 144:6 189:1 196:9,20 216:20		Laboratories 1:4 3:4 5:13 6:23 9:20 10:9 16:23	latent 18:18
know 7:13 11:7 24:8,9,24 25:14 26:18 27:20 27:25 28:15,24 32:15,21 37:5,9,12 37:14,22 38:11 43:5 51:15 52:24 53:11 53:20,21,22 59:1 66:1,4 67:14,25 73:9,14,15 74:9 75:1,7,10 76:8,11 76:13,22 77:9 79:21 81:1,6,8 82:4 83:11 83:15,23 85:14 86:24 87:1,10,12 88:3,9 89:5 92:6 97:25 102:4,7,12,14 102:17,19 107:20 107:22 108:2,10,10 108:24 115:6 116:13,15 117:1,2 118:2,5,7,8,22,23 118:25 119:9 120:15 121:16,25	knowing 143:2	laboratory 10:10,10,11 20:18 22:21 76:9,14 79:24	Latin 16:17
	knowledge 9:16 12:6 31:20 32:24 64:9 110:3,5 122:25 196:1	labs 179:24	law 3:16 25:8,9 45:18
	known 68:4 81:3 83:19 90:6 118:9 120:21 123:25 133:3 134:17 143:7 148:12 173:8,9 184:21 190:2 191:11 192:3,3,21 192:22 194:7 196:10,13 197:12	lack 19:15 214:20	lawyer 212:23
		LAL 84:8 86:12,14 87:21 87:21,23 88:18 156:25 160:20,21 160:23,24 161:7 164:18 165:5,12 168:1 175:9 177:20 178:7 179:20 180:10 182:10 206:17	lawyers 14:2 25:13
		LAL-based 175:22 176:4,10,18 177:12	lay 6:18
		LAL/TAL 88:12	lead 28:1 69:12
		lambda 48:5 53:14 106:19 110:10	leap 153:24
		lane 61:21 62:16,24	learn 28:19
			learned 21:17
			led 70:14
			left 127:5,15
			legal 4:16 24:19,21,23,25 25:6,8,15,17 37:19 39:4 49:7 55:13 96:11
			legend

146:11,12	46:2,18,23 47:6,18	59:18 60:13 105:23	4:9 5:23 7:20 8:21,25
length	47:21,24 48:9,14	155:7 213:25 222:2	9:5,10,15 27:10
115:10 136:4 150:19	49:15 50:3,12,14,23	222:5,8,11,14,17,20	37:4 39:17 40:19
150:24	51:5,7 52:25 53:5	223:2,5,8,11,14,17	41:2,21 45:14 46:20
lens	54:12 55:17 66:16	223:20	48:25 49:22 51:1,25
147:15	66:21,24 74:13 90:7	lines	52:12 53:8,19 55:10
let's	91:23 92:4,11,21	18:12 57:22,25 58:18	58:15 70:4 71:19
52:3 61:22 62:22	93:1,10,23,25 96:17	59:15,16 60:1,12	72:20 73:5 76:18
66:25 89:22 110:5	97:5 99:19 100:6,11	67:10 112:5	77:20 78:21 79:15
112:5 113:25 133:1	100:19 101:13	link	83:4 86:23 87:19
138:16 190:15	104:8 105:7 106:20	199:17	89:3 93:2 100:17
197:12 198:18	107:10 110:18	list	105:2,9 106:8 131:2
202:2 207:17	111:12 112:3,7,12	125:6,9,10 186:15,21	131:13 135:12
leucine	112:16,18 114:7	186:23 187:1,17	136:13 147:10
139:25,25 140:1	119:10 120:8	207:7	155:6,25 157:13
level	124:24 125:15,24	listed	161:12 162:22
33:1 141:22 151:15	126:2,4,13,18,24	26:12 28:5,22 74:2	169:14 170:13
170:24 183:5,10	127:6 132:15 133:6	208:16	171:9 172:14
192:3	133:23 134:6,21	listing	174:13 176:24
levels	135:9,22 136:11,17	115:20 116:13	177:22 182:6,24
130:14	137:5,10 138:14,18	listings	187:20 189:9,19
Lewis	138:25,25 139:16	47:20	191:15 192:17
3:16 4:9 5:23 14:2	142:8 143:7 145:5,8	lists	193:6 194:18 195:4
LGL	145:13,18 146:1,8	16:4 115:22,25	196:2 200:10 204:4
139:8	146:10,23 148:5	116:19 126:14	204:14 205:15
library	152:5,9 153:13	208:3	206:20 207:14
48:5 96:4 106:19	154:21 155:3	literature	209:14 210:2 211:7
110:10	156:25 157:5,11	30:14 187:11 195:22	212:12,21 213:8,18
License	164:25 165:13	196:22,23 197:3	215:24 217:6,20
220:21	171:22 172:8	little	219:6
life	173:24 176:10,18	6:13 7:12 32:17	location
108:21	184:25 186:5,9,14	51:25 70:5 83:2	19:2 111:24
light	186:17,20 187:16	87:8 104:1 110:15	logical
137:21 140:7 151:11	188:7 190:6,10,19	146:24 148:5	216:23
likelihoods	191:11,17 192:12	199:20	long
108:17	193:5 195:15 197:8	live	23:1 65:18 87:6
likewise	197:9,11 202:13	5:19,20 77:6,6,7	103:16 130:6
17:2 62:15	205:2 206:23 207:6	LIVENOTE	186:15
limitation	207:8 208:17,22	4:16	longer
41:15,18	210:23 212:6,19	livestock	110:11,15 140:8
limitations	213:5 214:16	182:12	186:23 206:24
35:10	215:10 216:15	living	207:2
limited	Lin	64:19	look
167:13 177:1 193:7,8	157:7 158:12 159:5,6	LLP	15:7,24,25 26:14,16
Limulus	159:14	4:9	28:9 31:4 34:13
17:8,8,9 45:2,5,9,12	line	Lo	47:7 57:1,4 61:20

66:14 71:10 73:18 77:11 88:3,4 101:5 102:1 106:1 112:5 112:24 114:1 116:22 118:22 119:11 123:1,24 125:4,13 127:9 133:19 135:3 136:16 140:3,23,24 141:2,5,22 145:22 146:9 149:24 156:6 158:22,25 163:20 164:5,15,24 174:6 174:18 175:5,11,15 176:3 177:11 180:3 183:8,13 186:3 190:1,14,21 202:15 202:17,18 207:17 208:1 209:25 210:8 210:22 211:25 212:13,25 213:10 213:21 217:12	105:24 losing 173:13 lot 32:19 64:14 82:6 105:10 110:12,12 121:19 167:24 195:16 210:20 lots 85:17 Loughran 2:4 4:4 5:6,10 9:3 13:9 14:25 27:15 37:10 39:19,25 40:23 41:10,25 43:22 45:24 47:2 49:4,25 51:9 52:2,7 53:15,24 55:25 58:21 65:8 70:11 71:7,25 72:23 77:10 77:23 79:8,16 83:6 86:4 87:11 88:1 89:11,21,24 93:7 95:10 100:18 105:5 105:15 107:7 111:5 124:17 131:4,8,22 136:7,24 148:3 149:10 155:20 156:14 157:24 161:14 163:10 168:9 169:18 170:17 172:6 173:2 174:15 177:9 178:9 179:18 182:15 184:8 187:23 189:14,25 191:5 192:8 193:1 194:14 194:21 195:13 196:8 198:18,22 200:20 204:9,22 205:21 207:3,16,20 207:25 209:23 210:5 211:24 212:16 213:2,11,24 216:3 217:10 218:10,16,18 219:7	Loverock 2:18 low 65:13 lower 66:9 204:17 LP 90:22 91:2 LPS 41:5,5,11,12,16,19 42:2,4,8,9 77:1 81:11 83:17,18,22 84:12 175:20 lunch 131:5,7,13 Luo 4:4 5:14 lymphoma 18:11,15 lysate 23:20 57:15 58:12,19 59:13 60:7 lysate-based 174:23 lysine 112:7	98:16 mammalian 56:7 57:14,22 58:11 58:17 59:11,16,23 60:6,12 201:11 205:24 mammals 75:10 managed 186:19 manner 31:25 40:22 74:21 76:3 89:9 91:20 94:2 135:23 144:14 144:15 155:13 170:3,9 171:25 172:10,21 179:9 193:13 manners 173:21 manufacture 87:6 mapping 102:11 149:20,21 150:9 160:10 marine 64:5,7,9 mark 70:17,18 marked 13:1,5 14:21 65:4 85:24 111:1 112:8 114:1 131:25 149:6 market 198:15 Maryland 5:20 Massachusetts 4:5 match 140:8 matches 123:25 125:7 material 41:23 materially
M			
MAGNA			
4:16			
magnesium			
54:19 56:20 60:19			
61:2,12 62:17 63:4			
63:15			
main			
42:4 60:9 181:11			
185:18			
major			
10:12 114:21			
majority			
181:15,21,23			
making			
46:1 88:4 174:5,5			
199:12,17 209:13			
216:7			
mammal			

117:25 118:3	184:7 185:6	135:17	144:20 146:22,22
materials	meant	messy	mischaracterizes
16:1 47:12 99:16	51:11 55:4,8 184:15	110:11	189:19 195:4 196:2
146:13	measure	met	209:14
math	58:24 59:5 89:8	11:9	misrepresentation
67:13 185:15,16	122:19 152:23	methionine	209:13
matter	198:11	112:6,8	missing
5:12 6:23 8:11 9:20	measured	method	98:2 138:25 139:17
16:22 20:5 25:3	41:7 50:2 79:25	106:17 137:25 138:1	misspoke
39:18 64:17 72:22	134:16	methodologies	138:9
73:7 98:14 117:8	measurement	176:10,18	Mizumura
163:1 218:6 221:4	51:15	methodology	26:19,23 34:18,24
matters	measurements	30:8,10,22 45:10	208:3
6:22 8:15 11:1 12:2	57:3 134:19 182:22	46:3,8 53:13 96:24	Mizumura's
12:20 72:18	measures	104:19 107:21	26:25
maximize	118:11 170:21	166:19 169:12	mL
108:4,20	measuring	methods	146:11,17
McClymont	56:17 80:20 81:10	21:6 53:14 109:22,25	MO
34:24 92:18 93:21	120:22	146:14 166:2	4:13
94:13 215:6	mechanics	metrics	model
mean	108:10	177:21	123:16,18,21,22,22
14:4 32:14 48:16	mechanism	mice	125:18,22,23,23,24
49:11 55:2,6 66:19	195:7 206:3,4 212:5	10:10,11,13,22	126:15,25 127:5,20
82:11 84:14 88:23	212:19	micrograms	128:3,9,10,15,17
89:5 94:6 97:21	mechanistic	146:11,17	129:7,19 140:23
121:2 122:12	174:8	microscope	142:1,9
125:21 134:23	medical	183:7	modeled
177:11,13 178:14	42:6 179:12,12 184:4	Mid	129:2
181:13 195:7	Medicine	24:4	modeling
196:12 211:11,13	96:4	middle	120:7,9 123:15
meaning	meet	96:22 127:6	124:19 140:19
60:4 80:6 121:8	84:23 203:11 204:20	midyear	models
188:1	meets	9:6	120:10 127:3 128:6
meaningful	204:19	millimolar	128:13 129:22
69:25 122:6 181:4,21	memory	54:18,19 56:19,20	modification
182:3,3	16:13 95:3 112:20	60:18,19 61:1,2	199:14 201:5,13,18
meaningfully	mention	63:4 203:14	201:24
130:18	49:23	million	molded
meaningless	mentioned	66:11 67:1,8,10	128:23
85:21	48:14,15 103:23	mind	molecular
meanings	194:16 201:12	215:3	19:12 20:9,14,17,19
37:19 87:24,24	mentors	minor	20:21,24 21:2 98:12
means	22:1,2	55:12	193:14
40:25 55:3 82:17	merely	minute	molecular-biology---
91:19 120:3 129:5	186:13	146:3 182:7	18:6
159:10 183:23	message	minutes	molecule

68:25 69:2 108:12 120:14 129:12,14 141:1,13 molecules 142:21 185:25 moment 47:7 month 9:8 months 109:16 Morgan 3:16 4:9 5:23 14:2 morning 5:7 53:25 131:13 Morris 11:5,8,9,11,13,18 34:6 motifs 199:4 motions 104:21 mouth 189:21 216:1 move 103:19 moved 142:4 movements 142:8 moving 122:12,14 mRNA 30:17 92:3,11 94:1,8 94:15 102:8 187:5 mRNAs 102:9 multiple 26:19 31:3 201:16 208:20,21 209:2 Muta 2:9 mutate 69:16 121:13 mutated 68:24 71:1 72:7 73:8	mutation 68:4 69:11 72:9 113:19 116:5 119:20,23 120:1,17 120:25 121:6,11 140:11 mutations 71:21 72:2,8 115:18 118:20 122:1 Muto 143:14 mutually 216:18 N N 3:17 4:10 114:7 name 5:10,14,15 11:5,24 17:13 20:23,25 27:17 159:1,1 named 26:12,18 50:10 names 9:17 narrative 164:12 narrower 39:15 205:13 narrowly 86:25 National 96:4 native 23:20,24 57:15,21,21 58:12,18 59:12,24 60:7 62:5 78:25 100:12 152:8 153:12,21 164:25 166:16 167:19 173:5,5 174:23 199:9,15,25 200:5 200:13 201:6,11 205:25 206:16 natural 77:2 138:8	naturally 42:2,5,7 132:21,23 167:23 nature 76:17 82:4 142:6 162:16 205:17,18 NCBI 91:9 99:16 near 185:24 nearly 96:21 98:20 152:12 187:13 near-complete 98:18 necessarily 22:14 27:17 84:14 116:20 153:23 154:3 162:21 206:19 213:21 necessary 19:25 64:9,17 92:7 necessity 68:7 98:9 need 7:13 20:2 22:14 45:19 50:21 71:19 97:25 98:8 101:1 110:6 136:9 212:25 needed 19:11 needs 75:18 neither 220:11 neutralize 72:16 never 6:14 10:24 11:9 22:19 23:3 64:13 81:23 98:4,6 108:8 108:9,17 121:9 183:14 new 54:2 72:12 NGN	140:12 Nine 62:9 NIS 139:24 nods 8:5 noise 181:2 nomenclature 21:11 noncoding 67:16,18 nonconservative 112:11 113:15,19 115:17 116:5 118:19 119:19,21 119:23,25 120:1,25 121:6,11 139:23 140:14 nonconservatively 121:14 nonconserved 111:21,25 112:2,3 115:24 116:9 117:8 119:5 nonidentical 138:23 nonrecombinant 100:3 nontargeted 91:20 non-peer-reviewed 32:8 normal 18:17 north 184:22 note 145:10 155:14 noted 21:3 notion 208:9 November 96:13
--	--	--	--

NST 139:10 140:2	47:17 137:17 148:16 148:21 149:2 193:18	46:25	20:2,8 21:3,6 23:11
nuclear 18:22		obtained 45:9 213:6	23:19 24:5,10,19
nucleotide 32:4 99:4 211:14,20		obtaining 45:21 216:5	25:17,20 26:6,14,18
nucleotides 98:13	O	obvious 34:18,23 215:23	27:3,6,16 28:3
number 13:2 14:22 16:4	oath 6:1 221:8	218:12	29:11,18 31:4,17
20:20 35:6 40:21	object 7:22 77:20 80:5,9	obviousness 34:9 35:17 214:2,7	32:22,25 33:7,12,17
57:17,17,18 58:16	83:4 100:17 211:7	217:1 218:11	34:8,17 35:8,18
61:9 64:7 83:17	212:3	occur 200:15	36:1,18 39:23 40:12
100:22 105:11	objection 27:10 37:4 39:17	occurring 42:3,5,8 132:22,23	40:24 41:15 42:9,14
129:4,22 134:14	40:19 41:2,21 45:14	occurs 142:25 154:24 155:4	43:16,25 44:3,7,25
135:15 136:21	46:20 48:25 49:22	October 90:7 94:20,25 95:19	45:11 53:4,25 54:6
137:18 146:6	51:1 53:8,19 55:10	95:25 109:10,10	55:5,7 57:1,13 58:2
151:12,16,17	58:15 70:4 72:20	188:8 208:24	58:22 59:9,20 60:3
152:13,15 153:1	73:5 76:18 78:21	Oda 208:3	60:14 62:2,3,15,20
157:20 158:3	79:15 86:23 87:19	offer 22:12 23:6 36:9 49:2	63:2,7,22 64:5,11
160:16 171:14	89:3 93:2 105:2,9	64:17 216:2 221:7	65:11,21 66:14,24
183:2 190:13 198:8	106:8 135:12	offered 23:10 64:10 188:2	67:8 69:7 70:17
203:4 205:12	136:13 147:10	offering 19:10,16	71:8 72:17 74:17,24
numbers 2:20 66:12 84:22	155:6,25 157:13	office 1:1 3:1 26:20 188:24	75:5,23 76:12 77:11
85:20 135:1 136:16	161:12 162:22	189:3,11	78:8,18 80:15 81:13
151:25 152:11	169:14 170:13	offices 3:16 209:2	81:17 83:25 84:13
157:12 159:8	171:9 172:14	oh 114:16 135:3 153:11	85:7,23 86:9 87:12
169:15 174:9	176:24 177:22	177:17 216:13	87:15 88:2 89:20
184:19,23 185:1,11	182:6,24 187:20	okay 6:9,14 7:1,10,25 8:7	90:9,13,18 91:22
185:12	189:9,19 191:15	9:4,9,19 10:13,19	92:9,17,25 93:8,13
numerical 147:13,25 174:2,3	192:17 193:6	10:21,25 11:3 12:11	94:23 95:3,11,15
178:16 184:14	194:18 195:4 196:2	13:10,15,17,19,25	96:3,7,12,15,25
numerous 187:2	200:10 204:4,14	14:15 15:7,17 16:15	97:6,10,15,18 98:17
N-free 137:16	205:15 206:20	16:25 17:4,9,10,14	98:22 99:9 100:5
N-terminal 137:19,20,21 138:6,8	207:14 209:14	17:15,19,20 19:5,18	104:2 106:3,4 108:1
139:3 148:15	210:2 212:12,21		111:6,8,11,22
193:10	213:8,18 215:24		112:21,24 113:6,16
N-termini 148:14 150:17,23	217:6,20		113:22,25 114:17
151:12	objective 27:25 218:2		115:2,16 116:2
N-terminus	Obst 2:17 64:25		117:20 119:11,22
	obtain 45:20 46:11 97:21		121:2 122:22
	159:17 186:14,16		124:12,13 125:3,13
	187:9,18		128:12 129:18
	obtainable		130:1 131:15,23
			132:4,11,20,25
			133:15,19 134:3,9
			135:7 136:8,25
			137:12,23,24
			138:24 140:18
			142:10 145:17
			146:5 147:6 149:16

150:2,7 151:4 152:19 153:10 154:12,23 155:3,21 156:15,24 157:7 158:12,17 159:5,5,8 161:8,15 162:1 163:11,22 164:5,13 165:21 166:25 168:10,19 169:3 170:10,18 171:3 173:9,17 174:12 175:11,21,25 176:9 177:10,17 179:2,23 180:3,8,13 181:5 182:16 184:9,16 185:10 186:8 187:25 188:23 190:9 198:18 199:8 199:17,22 200:8,21 202:2,8,11,21,24 204:10,23 205:1,8 205:22 209:1 211:5 211:25 213:25 214:6,12,25 217:15 219:2,5 older 70:23 Omega 117:2,9,16,16 once 45:21 ones 69:5 92:23 93:4,5 129:20 134:6 137:8 190:23 one's 27:21,22 open 101:9 open-ended 42:20 126:20 206:22 operating 6:19 operation 84:3,5 opine	91:6 opined 208:7 214:2 opinion 27:6 31:5 33:7,13,16 39:14,18 44:11 49:2 75:5 80:2 81:19 94:23 107:15,16 163:8 176:13 188:3 204:11,11,13 209:10 214:19,19 214:25 216:2 opinions 12:12 19:10 22:13 23:7 31:18 32:25 33:2,10,17,20 34:3 34:4,5,8 35:2,3,5,7 35:9,14,18,24 36:9 37:2 38:9,13,19 39:8 42:18,24 43:6 43:11 44:7 64:10,17 65:22 189:8 202:4 208:9 210:12,20 216:5 opportunity 168:25 opposed 216:18 opposition 107:17 optimally 30:9 optimizations 30:13 optimizing 30:12 options 60:14 oranges 172:18 order 22:12 41:20 97:8,19 104:11 108:4 123:3 189:6 206:4 217:16 ordinary 25:23 26:3 217:25	218:4 organic 27:4,7,13 organism 103:13 original 105:12,13 originally 216:25 other's 14:6 outcome 70:9 189:2 220:16 outlined 148:1 output 124:20 125:4 178:16 outside 27:10 29:7 39:17 41:21 48:12,25 123:9 155:7,25 189:10,20 194:18 205:6 209:15 210:2 211:7 212:12,21 213:8 215:24 overall 68:24 116:21 142:20 157:22 overlaid 128:13 overlay 127:6,11 128:17 owner 1:8 3:8,11 4:8 6:23 8:11 9:11 17:2,4 28:22 36:2 owner's 29:14 33:8 oxygen 108:11 O(1.2.4) 2:23 P page 2:3 6:19 13:11 15:7	16:16 34:14,22 40:9 57:3 66:15 78:16 84:3 86:10,10 88:4 95:16 97:11 112:25 113:4,5,7 119:12 127:4 128:22 133:13 141:8 158:24 159:3 161:4 161:5 163:21,23 164:16 168:15 175:7,15 177:12 180:4 208:1,2,2 212:1 214:3 217:13 222:2,5,8,11,14,17 222:20 223:2,5,8,11 223:14,17,20 paired 122:23 123:6 panel 146:7,8 paper 143:13,13 145:12 157:23 162:5,6,10 163:3 167:8 168:3 173:4,7,10 182:4,25 papers 70:15 paragene 139:24 paragraph 14:15 15:25 17:22 25:20 26:1 29:3,4 31:4 34:14,15,22 56:1,15 65:11,12 73:19 74:2 78:4,5 80:17 88:18,22 90:23 106:2 108:1 113:7 124:22 133:1 133:3 149:24 151:23 152:1 156:16 160:5,5 161:4,5,6,18 164:16 168:10 169:16,17 174:18 177:12 179:14 186:3,21 190:1 192:19
---	---	---	---

194:19 195:24 196:4 199:1,2 202:2 202:3 210:22 211:25 213:12,22 214:12 paragraphs 199:1 parameter 132:8 parameters 128:2 153:16 192:24 216:16 paraphrase 217:9 parcel 38:14 parentheses 134:17 part 20:15 35:21 38:14 116:17 117:10 129:12,13 139:3 152:25 164:12 195:11,11,12 210:16 partial 98:3 137:1,13 138:19 participate 9:2 particular 18:2 21:15 22:14 23:9 51:19,21 59:7 68:13 70:23 71:14 73:4 83:21 91:12 98:10,10 102:11,12 120:12,17 122:9 132:12 134:15 163:5 165:10,17,18 167:15 170:11 171:14 173:4 174:1 180:11 181:7 188:6 201:14 particularly 19:12 30:15 61:14 68:14 79:2 106:9 135:24 136:3 181:4	parties 220:12,14 partner 199:4 parts 14:5 passed 210:24 patent 1:1,2,7,8 2:6,8,14 3:1 3:2,7,8,11 4:8 6:15 6:23 8:11,16,17 9:10 13:3 14:23 17:2,4 21:4,13,15 25:8,9,13 26:12,20 26:21 28:22 29:13 31:6 32:22 33:8 36:2 39:21 40:2,6 40:17 41:11 44:14 45:16,18,19 50:5 51:12 58:4 93:10 99:16 105:12 107:17 118:25 123:12 159:12 160:2,2 188:2,24,25 189:3,7,12,13,23,24 201:8 202:5,17,18 206:10 209:2 212:11,23 213:4 214:3 218:3,7 patentability 37:3 patentable 206:5,6 patents 12:17 19:11 25:11,12 25:13 44:4,19 50:16 105:3,4 109:13 188:21 208:4 209:21 210:19 patent's 217:23 patent-related 123:13 pathogens 75:22	patient 178:23 patients 42:7 pattern 191:21 pause 140:5 pay 119:4 162:23 PC 4:3 PCR 19:1 30:9,24 48:6,6,7 48:8 53:13 96:24 97:3,22 98:4,6 103:7,11,22 106:16 106:21 107:1,2 108:25 159:16 PCRs 98:1 103:14 PCR-derived 103:13 PCT 2:7 34:19 93:18 105:16 188:20 207:10,17,22 peak 154:23 155:4 peer-reviewed 32:6,18 92:5 162:20 211:15,22 pen 137:23 penalty 221:2,3 pending 7:15 penultimate 182:9 people 81:2 184:3,4 peptide 47:10,16 108:3 139:3 150:3,9,19 151:1 159:15	percent 6:12 54:17,18 60:17 60:18,25 61:1,11,11 61:13,14,23 62:2,9 62:22,22 63:1,3 66:11 67:8,11 108:9 108:18 109:3 128:22 130:15 139:14 151:2,15,18 152:5,8 154:25 155:4 157:4 158:15 160:8,12,15 168:16 168:20 169:1,2,10 169:10,13 171:1 172:1 175:13 180:21 184:18,20 184:20 185:2,3,19 185:22,24 202:14 202:22,22,23,25 203:4,10,13,17 204:23,24 205:3,5 205:12 percentage 151:19 percentages 184:17 perfect 183:16 perfectly 175:8 perform 30:15 42:23 45:22 81:25 97:22 159:15 performed 98:24 147:16 155:12 performing 42:11 82:13 175:9 performs 126:10 129:12 period 104:23 182:1 perjury 221:2,3 person 25:23 26:3 27:6,7,9 27:12,22,23 28:4,10
--	--	--	---

29:19 31:20 33:3 91:1 96:15 117:20 147:6 157:16 158:8 158:20 160:14,15 163:3 183:3 208:11 218:4,4	pharmacopeia 82:9 pharmacopeial 84:25 87:16 89:13 pharmacopeias 74:15 81:4 82:10 84:6 89:6 173:13,14 178:18 179:13 181:25 183:20	210:16 placed 5:25 184:4 plasticity 108:24 please 5:16 17:21 56:2,4 71:20 plus 48:4 PNAS 31:1 point 7:3 12:22 33:21 34:11 35:11,21 42:13 47:3 50:13,22 70:20 77:21 78:12 81:3,8 92:15 94:18 103:3 106:14 114:24 120:2 121:5 135:24 144:24 145:2,3,20,21 149:22 151:22 158:21 160:1,17 166:4 167:17 168:3 168:15,25 170:1 173:10 180:18,22 183:20 185:4 186:11 188:18 196:7 201:15,23 215:23 pointed 113:11 216:19 pointing 67:3 84:14 173:4,6,7 points 122:23 182:19 183:1 201:16 polymers 98:14 polymorphisms 141:2 polyphemus 17:8,9 45:2,5,12 46:2 46:18 47:6,21 49:15 50:3,14,23 52:25	53:5 54:12 55:17 66:16 90:7 91:24 92:21 93:1,23 96:17 99:19 100:6,19 101:13 104:8 105:7 107:10 110:18 125:25 126:18,24 137:6 145:13,18 148:6 152:5,9 153:13 156:25 157:5,11 164:25 165:13 176:11,19 187:16 190:6,10,20 191:11 195:15 202:13 205:3 207:6 210:23 212:6,19 213:5 214:16 poorly 18:10 portion 193:10 portraying 209:11 POSA 27:13,19,23 28:2,6,9 28:21 29:2,13,20 31:9 32:11,17 33:6 33:11 35:19 45:7,20 46:7,24 47:15 48:2 50:6,19 51:5 53:1 53:11 55:3,7 66:1 80:23 81:8 90:20 91:4 97:19 102:16 102:19,20,21 104:14,16,21 106:5 106:11 107:5 108:2 109:1,6,7,20,24 110:2,4 118:14,14 118:14,17,22,25 119:2,5 120:4,16,23 122:21 134:22 135:2,16,18 139:15 139:19 140:3,6 143:4,6 144:7 147:13,19 154:5,7 155:21 159:11
personal 157:7,18 159:2,13 162:13 163:1 persons 31:13,15 163:3 217:24 person's 28:1 perspective 118:15 147:12 186:1 216:20 218:4 pertained 195:17 pertaining 3:14 46:23 pertains 57:24 156:4 petitioner 1:5,12 3:5,11,13,15 4:3 5:12 9:19,22 10:5 16:22,25 petitioner's 33:9 PGR 8:17,18,20 14:21 15:2,6 33:4 65:5 73:23 90:11 91:7 132:1 149:12 156:17 219:4 PGR2025-00023 14:23 ph 139:24 phage 48:5 53:14 106:19 110:10,13 phalein 141:17 pharmaceutical 74:10,15	phrase 17:18 27:20 31:21,22 40:24 41:12 74:4 82:21 83:1,8 93:14 phrasing 59:2 Phyre 2:24 120:9 124:20 125:4,6 126:7 128:21 130:21 140:19 141:24 142:7 Ph.D 1:11 2:2,16,20 3:12 5:2 13:2 14:22 17:23 18:2,4 19:6 19:19 20:8,23,25 21:14,16,24 26:7,25 27:4,7,17 28:4,15 28:16,19 30:11,25 92:17 221:10 222:23 223:23 Ph.D.s 28:5,22 pick 26:11 picked 70:22,23 picture 127:15 piece 124:10 171:10,12 pieces 104:1 121:24 pipetting 82:4 place		

162:19,23,25 163:4 164:22 167:2,3 171:13 181:19 185:12,19 187:7 191:24 192:23 195:1,21 196:1,7,22 197:1 206:7 209:24 210:8,14 215:21 217:18,25	preamble 100:20 209:21 212:15 precedence 164:9 precise 38:15 40:22 41:3 152:14 160:11 169:12 precisely 179:9 preclude 28:6,21 29:19 precursor 138:3 predated 117:16 predating 117:15 predict 215:15 predicted 120:13 124:23 126:17,23 127:18 128:6 142:8 prediction 123:23 171:3,7 predictions 117:22 154:8 155:22 predicts 128:16 prefer 61:3 79:22 214:9 preferred 124:5 premarked 13:1 15:2 40:2 43:18 86:1 95:4 premise 189:9 prep 166:16,16,18 167:19 preparation 12:12 30:20 167:9,10 172:25 213:16 prepared	16:11,12,14 167:7 170:3,9 172:20 prepares 87:4 preparing 25:18 43:9 57:8,10 166:8 presence 54:18,19 60:18,19,25 61:2 63:3 153:25 203:1,10,13 present 30:23 46:23 47:1 88:12 123:5 169:16 188:1 193:20 212:3 presented 77:12 106:10 presents 195:16 preserve 68:13 presumably 77:5 146:16 pretend 110:5 pretty 54:9 117:17 129:23 135:6 143:15 146:19 180:19 183:3 184:7 previous 209:21 210:19 previously 18:7 25:12 117:5 primarily 18:4 74:5 145:4 prime 30:16 107:3,3 108:3 108:3 primers 48:7 103:7 106:25 107:2 159:16 primitive 75:11,12 principally 88:10	principle 142:16 principles 20:13 24:23,25 25:6 prior 9:9 12:20 35:9,20 67:1 128:4 143:13 priority 31:7 33:15,18,19 34:2,5,7,10 35:16 91:5 94:7 105:13 109:13 117:3 130:22 187:3 188:8 189:23 195:21,23 196:7,25 208:23,24 215:3,11 probability 108:4,11,17,20 probably 6:11 16:23 70:22 102:1 152:12 167:7 probe 99:7 106:18,18 probing 110:10 procedures 97:19 98:8 177:13,20 proceeding 219:9 proceedings 156:2 process 85:5 processes 29:7 proclotting 98:23,25 99:6,11 110:18 produce 56:8 193:20 196:10 196:24 197:1,5,7,10 197:23 206:12,13 produced 18:23 22:4,5,7,9 50:4 50:15 54:13 56:24 57:14,20 59:10,17
--	---	--	--

61:6 62:21 63:14,25 79:5,7 164:18 165:6 165:6 166:3,18 167:23 176:1 199:23 200:3 202:12,16,24 205:1 205:2 206:16 207:6 producing 46:4,5 58:11 product 103:6,19 183:13 production 22:11 29:7 46:18 86:15 198:1 205:24 206:1 products 183:13 186:18 Professional 3:19 4:13 220:4 profile 194:12 program 18:11 20:11,12 114:17,23 127:24 programs 18:20 projects 22:23 91:19 promiscuous 150:16 promoter 18:7 19:1,3,4 21:22 properties 76:10,23 111:18,20 114:4,25 163:14 215:17 property 73:17 76:5,9 79:23 123:10,12 proportional 180:4,19 181:11 proposed 28:5 36:12 54:2 proposes 28:23 prosecution	26:20 protease 41:7 83:18,19 119:13 129:13 141:12 142:11 144:13 148:2 150:15 191:12,20 194:8,11 195:17 200:16 201:25 proteases 142:18 150:15 190:3 194:4,16,25 195:3,5 195:11 protein 18:8 23:12,13,21 29:7 40:13,16 47:24 49:14,19 50:4 52:19 54:11,13,15 55:15 59:25 60:15,16 61:7 63:25 69:14,15,18 69:20,22 70:7,7,8 70:25 71:17 72:13 73:4,8,13 79:1 80:1 85:3 87:4 91:12,17 92:3,11 93:11 98:11 99:4,15 100:10 101:15,16,24 104:17 106:22,24 111:12 119:24 122:3 124:4,5,6,8,9 124:11 125:8 129:2 129:3,5 137:16 138:4 141:21 143:8 143:25 150:12,18 151:6 152:7,9,13 157:1 159:20 164:1 166:6,7,8,10 167:5 167:6,21 171:22,23 171:24 172:16,16 172:18,19 173:12 173:12,16,16 176:1 187:5 193:12 197:15 199:15,16 199:19,23 200:1,3,5 200:13,14,15,17,18 200:22 201:6,7	202:12,24 205:1,4,9 206:8,16 proteins 19:6,20 20:3 22:4,6,8 22:10,11,13,15 42:24 43:2,3,4 46:1 46:4,6,8,18 48:9,21 48:22 50:15,24 67:21 68:8,10,13 69:10,23 70:14 74:6 77:14 78:10,19 80:4 80:21 81:1,6 86:20 86:20 98:5,7,10 99:1,10 116:22 120:19 122:4 123:15,16 129:9 130:6 132:5,12,17 132:18,22,23 133:5 152:24 159:19 161:10 165:23 167:6 170:9 171:4,7 172:20 173:9,15,20 173:21 180:16 186:5,20 190:2 192:12 193:13 197:16,21,24 199:4 199:10,11,14 210:25 212:5,6,18 protein-protein 71:5 proteolysis 201:4 proteolytic 193:8,8 195:15 protocol 30:8 protocols 208:21 prove 104:21 provide 20:4 29:12 34:8 44:8 45:1 48:10 63:12 193:25 195:1 212:4 217:17 provided	12:23 56:14 57:2 157:10 provides 31:9 44:12 60:14 provisions 3:14 pseudomonas 176:4 178:4 PTAB 192:11 public 48:4 93:4,6,14 94:10 157:21 publication 2:9 30:1,5 47:12,16 70:23 91:23 92:5,6 92:10 93:1,19 99:21 132:19 134:11,13 149:12 150:25 152:22 157:16 158:13,22 159:9,9 159:13 160:4,19 163:5 164:14,23 169:6,22 180:14 181:6,8 196:20 208:8 210:1 211:15 211:22 publications 31:3 32:23 92:20 93:22 94:12,14 152:2,10,16 184:18 186:4 197:13 209:19 210:18 publicly 92:6,8 95:25 187:4 187:14 198:16 publish 159:21,25,25 published 28:17 30:25 32:3,5,7 32:14,17 46:13 48:2 48:4 70:15 91:5 92:4 93:10,18 94:10 94:19 95:19 96:6,8 109:10 110:7 145:14 159:23
---	---	---	---

168:22,24 169:6 182:4 186:17,22,24 187:4 188:17 198:16 publishing 32:20 pulling 101:8 purchased 10:13 purchasing 10:21 pure 59:8 77:6 80:1 147:4 purified 59:18 74:7 81:1 122:4 132:17,24 147:4 153:17 165:19 166:1,6,17 167:5 168:1 170:4 171:18,22,23,23 172:8,8,8,16,16,18 173:9,11,12,15,16 173:16,20,20 178:19,24 purified-enzyme-b... 177:7 purifying 68:5 144:24 purity 85:16 87:5 purposes 3:13 19:10 55:13 84:9 pursuant 3:14 pursuing 36:2 put 41:15,18 42:7 45:11 45:16,19 46:16 53:17 61:16 71:9 83:15 95:24 120:15 128:21 214:1 putting 14:10 16:5 121:8	189:21 216:1 Q qualifications 64:7 qualified 29:1,13 qualifies 27:18,22,24 212:24 qualitative 174:8 quality 96:22 139:4,5 140:9 210:10,14 quantitative 170:21 quantitatively 89:17 177:20 205:18 quantity 196:23 quantum 108:10 query 99:4 question 7:6,7,15,16,22,23,23 7:25 9:24 19:11,13 19:19,22 33:24 37:6 37:23 38:17,22,23 40:22 42:1,21,21 49:5,6,7 50:21,25 51:2 53:23 69:4 72:21 76:2,3,20 78:23 79:9 80:7,10 80:13 83:5 84:24 91:13 94:11 116:2 126:20 136:10 140:22 142:14 147:12 156:10 157:15 176:16 189:10 191:8 197:19 199:21 200:11 206:21 214:11 217:11,15 questioning 105:23 144:18 155:7	questions 2:4 5:6 6:20 7:1,4,19 8:5,7 19:25 33:23 71:6 131:24 187:3 214:1 219:1,7 quick 89:22 198:19 218:16 quickly 97:4 104:19 108:22 108:23 147:23 187:9 quite 10:11 19:8 51:14 75:10 127:13 130:16 quote 40:13 quoted 133:9 161:16 quotes 101:1 R rabies 2:12 71:14,24 72:3,7 73:9,12 RACE 19:1 29:23 30:9,12 30:15,24 48:6,7 106:21 107:2 108:3 108:3,25 ran 129:19 137:23 177:23 random 122:1 range 75:15 155:14 180:24 194:3 203:6,18,19 203:20,21 204:1,5,6 204:11,16,24 205:5 205:7,13,19,19 206:25 214:18 ranked 126:11 ranking	116:12 rank-ordered 125:9,10 126:14 rapid 31:25 rapidly 32:12 rarely 171:11,11 rate 14:17 65:19,21 66:11 147:1 rates 65:13 ratio 154:15 reaction 76:24 77:2 reactions 103:11 read 11:14,16,20,22 12:7 12:10 25:17 36:15 36:16 51:11 54:8 55:11 58:2 60:16,21 95:12 96:23 102:4,7 102:17 118:25 152:2 162:4,19 164:22 196:23 203:4 214:9 217:7 221:4,5 readily 53:12 reading 11:17 101:9 118:17 139:15,19 147:13 163:22 194:19 208:11 217:21 reads 96:8,16 98:19 102:3 102:6 103:17 162:25 reagent 122:16 168:1 178:24 196:16,24 reagents
--	--	--	--

22:21,22 23:17,19 82:1 86:13 87:2 88:9 89:6,13 173:19 173:19 175:8 177:2	53:21 87:3 146:6 147:25 166:12,15 167:1 169:21,24 208:20	9:7 38:8 55:21 99:22 180:2 197:25	112:10 127:12
real	recall	recombinant	redirect
76:10 168:4 181:2,3	23:20,22 28:16 33:5	23:21,25 46:1,17	219:4
realistic	47:9 54:4 63:18	49:18 50:24 60:2	reduced
183:17	64:3 66:12 75:3	79:2,3,4,5,7 81:6	220:10
realize	90:16 92:14 93:3,8	88:9 105:7 132:5	refer
209:1	93:12 99:12 107:24	152:6 153:5,6,17,21	16:21,23 17:3,8,13
really	115:22 123:14	154:15,24 157:1	24:16 25:2 26:1,6
9:7 19:11 20:20 21:2	132:9 152:25 180:1	165:2,7,16,20 166:1	29:23 31:19 44:1
23:9 25:15 32:19	184:25 195:18	166:6,8,18,19 167:6	58:19 90:24 93:17
33:10 35:25 37:5,8	198:14,17 206:2	168:2 170:5 172:19	123:21 137:25
37:22 38:16 39:5	207:15 209:20	174:22 176:11,19	reference
49:8,11 73:13,15	received	178:7,18,23 179:20	2:11 11:4 17:11
76:8,22 80:6,9	21:3,13	180:9 182:11 189:5	28:12 42:13 87:15
81:24 89:5 103:18	receptor	189:16 197:14,15	123:15 131:16
117:11 118:22	73:11	198:1 199:11,15	132:1 190:9 191:16
132:17 141:24	recitation	200:14,15,17 201:6	210:17,18
157:14 163:1,4	55:1	201:10 205:24	referenced
166:2,23 170:14	recite	206:1,8 212:4,18	47:13 48:9 131:15
172:3,3 178:3 181:1	203:12	213:5,7,14 214:15	149:6 194:25
181:13 184:5	recited	214:17 215:6	references
192:18	55:22 56:9 169:15	218:13	35:9,20 105:21
real-world	204:23	recombinantly	151:24 162:14
178:21 181:21	reciting	22:3,5,7,9,11 50:4,15	191:10 195:25
reason	54:10	54:14 56:24 57:14	209:20 210:18
6:6,8 18:9 24:11,17	recognition	57:20 59:10 60:6	referred
35:19 65:19 66:6	71:22 75:14,15 83:18	61:6 62:21 63:14,25	24:22 74:24 88:10
67:7 85:17 95:2	83:21	176:1 197:2,11,23	referring
97:25 103:23	recognize	199:22 200:3,22	16:25 17:4,9,14,19
104:13,20 107:19	15:3 40:4 43:23 65:9	202:12 205:2 207:5	24:24 71:22 78:13
110:4 120:4 122:17	72:4,5,16 78:8	recombinant-based	83:10 84:2 90:13
167:14 186:25	83:17 86:7 95:6	176:6 177:6	97:13,16 110:23
187:7 199:12	104:24 111:6,7	reconcile	172:11,12 187:21
200:24 201:4,9	123:4 140:10,14	79:10	197:19 199:9
208:19 216:23	149:14 156:21	reconciled	207:22
222:4,7,10,13,16,19	164:5 168:12	214:20	reflect
222:22 223:4,7,10	177:10 188:19,22	record	134:19 163:2
223:13,16,19,22	207:23 218:5	5:16 52:4 131:6	reflected
reasonable	recognized	recorded	141:20
122:8 154:6 155:2	73:2	8:6	reflective
reasonably	recoiled	records	142:19
159:11 214:14	82:24	90:14	reflects
reasons	recollection	recovered	115:14 125:10
		198:5	refresh
		red	16:13
			refuse

80:10 regard 130:16 192:2 regarding 15:6 19:13 26:2 116:4 145:10 179:12 195:2 202:9 region 97:17 120:12 141:13 regions 113:8 138:21 199:3 Registered 3:18 4:13 220:4 regulate 181:25 regulating 183:21 regulators 21:7 relate 29:6 166:12 related 8:15 19:5,10,20 20:16 21:16 32:16 35:16 43:3 49:3,8 74:11 76:6 77:3,5 115:25 158:9 172:3 185:9,21,24,25 208:9 209:5,8 220:11 relates 8:17 relating 14:23 relation 6:14 relationship 9:10,13 77:8,9 79:18 80:15 143:9 relative 22:24 59:7,12 85:1 85:11,22 133:25 139:1,17 200:5 201:11 220:13 relatively 24:2 103:8 109:1	147:21 163:8 164:9 relativistic 184:15 210:12 released 116:25 relevant 18:13,16 20:4 27:14 179:13 193:17 relying 95:23 116:3 195:25 196:1 remainder 144:3 210:1,7 remarkably 142:21 remember 10:5 29:24 64:4 67:14 99:14,17 166:19 189:1 213:20 remind 146:4 render 72:3 repeat 91:13 164:3,11 176:16 repeated 164:8 rephrase 7:5 40:21 49:9 76:3 80:13 report 30:18 92:10 151:1 153:4 160:19 164:11 169:9,10 210:24 reported 1:19 100:4,23 102:1 103:24 136:11 138:12,24 145:9,25 149:19 156:7 158:15 160:8,9 168:16 169:12 170:12,23 171:1 184:17 185:11	186:5 reporter 3:19,19 4:13,13,14 4:14,15,15,16 7:12 8:3,6 9:25 18:14 220:1,5,5 reporter's 16:19 reporting 144:19 160:12 165:10 reports 135:8 145:17 159:6 173:24 186:8 represent 5:12 124:3,9 representation 113:9 representative 26:13 47:25 represented 5:21 135:21 reproduce 57:3 100:15 require 7:15 30:5 40:15 89:15 200:11 required 6:3 29:8,11,16,18 46:25 69:24 75:1 76:24 144:12 206:4 requirement 62:13 63:3,6 179:6 217:23 requires 40:13,18 49:13 99:3 requisite 29:12 research 18:3,4 19:5,20 21:14 21:16,18,19 30:4,19 30:20,23,24 42:23 70:12 71:11 researchers 24:7 90:14 91:3,11 91:15 94:19 169:22	174:20 179:23 reserve 219:3 residual 50:3,13,17,22 51:4 51:11,13,22,23 54:16 55:19 56:18 57:15,20 58:10,23 58:24 59:2,4,11,12 59:17 60:5,11,15,17 60:24 61:7,10,22 62:4,16,21 63:13,24 75:23 76:4 78:10 79:4,10,12,23 80:19 132:7,10,19 144:19 144:21,22 152:23 153:24 155:22 156:2,3,13 200:4 201:10,19 202:13 202:25 203:9 205:3 205:25 206:15 214:17 215:16 216:11,15 residue 112:2 133:16,22,25 140:11 141:16,18 141:23 142:11 148:22 residues 112:10 117:19 122:24 137:5,9 139:7 140:2 194:2 195:5 resist 132:13 resistance 58:25 resources 31:24 119:6 respect 68:16 71:8 91:10 100:13 102:2,3,10 134:5,18 135:8 161:24 202:4 205:8 218:11,13 respectively
--	---	--	--

143:24 164:1	revealed	86:22 87:13 88:6	207:6,10 208:4,8
respects	151:1	89:16 90:7 91:7,12	209:3 215:8 216:6
135:3	revealing	91:17,25 94:20	218:15
response	150:4	96:18 98:5,19 100:7	right-hand
32:20 71:24 72:4	reverse	101:14,24 102:18	159:4
73:14 81:11 155:9	102:9	104:5,9 105:1,8	rigorously
214:11	review	106:7 107:10 108:7	129:21
responses	15:15 16:8 24:17	109:6,10,14,17	rise
177:14	25:19 28:1,12 30:6	110:20 115:18	44:4 58:3
responsive	30:7,22 37:8 71:20	118:16,21 119:24	River
148:2	118:18 182:7	121:7 122:13	1:4 3:4 5:12 6:23
responsiveness	213:16	123:16,20 125:16	9:20 10:6,8,9,14,15
161:19	reviewed	126:4 127:7 128:8	10:17,22,23 16:23
rest	16:1,5 27:1 36:11	128:10 129:2 130:1	16:24 43:18 107:17
151:23	39:3 57:7,10 63:12	130:3,8,12,20 132:5	RNA
result	213:19	132:8,22 133:23	98:14
82:13,16,16 85:10	reviewing	134:1,7,9,21,24	room
89:7 106:11 157:22	13:17	135:11 137:2,6,10	108:12,13
164:24 178:25	rFC	137:14 138:14,19	rotundicauda
179:3 183:25 184:2	88:5,10 160:20,22,23	139:1,18 140:12,15	17:17 152:4,7 174:22
184:14,14	164:19 165:15	140:16 141:21	roughly
resulting	175:25	142:12 144:19	67:9
77:1	right	145:19 146:2 149:4	row
results	6:4 7:3 8:14 11:1	149:21 151:6	62:23 114:1,12
2:24 30:19,24 63:13	12:22 13:4 15:24	152:17,24 153:8,14	119:12 140:2
71:11 81:12,15	16:6 19:7,21 20:5	153:22 154:16,21	RPR
89:14 117:18	20:10,24 25:4 28:7	157:1,3,12 158:13	1:19 220:20
120:16 130:17	29:14,20 30:3 31:14	158:16 159:7,21	rule
143:22 144:5	31:20 33:12,15	162:3 163:14	32:9 167:17
149:19 154:12,20	34:10 37:3,13 38:2	165:13,16,24	rules
155:7 161:21,24	38:7 39:9,21 40:14	168:23 169:7,13,23	3:14 6:18
162:3,5,24 163:6,18	40:18 41:1,11 42:3	170:12 171:8 173:3	run
163:23,24 164:2,8,8	42:10 44:1,5,9,19	175:6,7,18,23 176:1	85:9,11,13 95:16
164:11,13,16 165:5	44:23 45:3,13 46:2	177:18,21 178:13	96:12 126:5 183:1
165:10 166:6,15	47:6,22 48:12,24	179:6,21 180:17	183:16 184:11
167:1 169:4,23,25	49:16 50:4 52:17	181:17 182:5,17,20	running
170:10 177:25	53:2 54:23 56:13,24	182:23 184:10,18	85:13
178:1,2 180:16	57:8,11 58:7 59:13	184:22 185:3 186:6	
retained	59:21,24 60:20	186:21 187:1,19	S
8:10 107:16	61:17 62:10,13 64:6	188:21 193:5	Sacks
retrieve	64:19,22 65:24	195:15 196:11,21	4:3 5:11
94:3	66:11,17 67:11	197:2,17,24 198:18	salmonella
retro	68:18 69:12 70:3,14	198:25 199:10,11	176:4 178:4
103:14	71:18 73:4 77:16,19	199:19 200:1,5,9	salt
return	78:2,11,20 81:15,18	201:13,20 202:9,20	56:18 139:21 156:5,8
182:11	81:20 83:14 85:4,12	203:2,11 204:24	156:10

samples 84:12,20 160:22 179:24,24 183:24	196:9 198:23 205:22 207:9 218:19,25 221:10 222:23 223:23	163:22 164:15 178:3 208:2	164:20,21 166:23 167:13 168:4,16,18 169:25 172:23 174:25 175:1 177:15,16 180:6,11 180:12 181:17,18 182:25 190:7,8,23 191:2 193:9,23 194:19 198:20 199:6,12 200:22 202:3,5 208:5 211:3 211:4 212:1,8,9,25 213:14 214:4,5,23 217:14
satisfies 61:7,17,19	scheme 66:4	secondary 128:2	seeing 23:16 114:10 132:9 137:19 201:9 206:2
satisfy 62:12 63:2,5 217:22	science 81:23 104:13 152:20	second-to-last 40:9	seek 100:14
save 221:5	scientific 25:16 28:24,25 37:17 37:20 49:11 163:5 182:25 183:4	secreted 197:21,23	seemingly 177:24
saw 58:11 153:18	scientist 41:3 98:2 142:16	section 16:1 25:22 30:10 34:17,23 56:7 152:2 162:5,6,18,19,24 163:7,17,18,20,23 164:6,9,14 165:18 166:11 214:5	seen 36:14 99:20 123:12 154:2 168:1 205:22
saying 29:15 70:6 73:1,6 74:18 76:7,21 80:22 83:15 103:16 105:22 109:2 116:13 126:23 142:16 147:6 158:7 160:15 176:25 178:11 182:2,17 184:6 187:18 207:15 208:15 211:19	scientists 108:8 121:9 196:18 196:19	sections 34:12 57:17 162:6 163:2 164:10 209:20	Seikagaku 1:7 3:7 6:24 8:11 9:11,14 12:13 17:2 17:3
says 13:11 21:6 33:25 34:17,23 41:23 54:22 60:23 62:1 67:6 86:12 95:19 128:22 142:23 143:19 146:16 157:4 161:7 163:5 165:5 177:12 182:13 203:13,22 216:8	scope 27:10 31:10 41:21 45:8 48:12,17,25 155:8,25 189:10,20 194:18 203:2,5 205:4,9,11 209:15 210:3 211:8 212:12 212:21 213:9 215:24 217:4,19	secure 212:20	Seikagaku's 28:5
scale 29:7 146:24	score 115:12	secured 160:3	selected 54:16 60:24 67:22,23 95:2
scenario 69:7	scorers 130:15	see 8:2 15:8 16:2,13 17:25 18:1 25:24,25 26:4,5,9,10 29:9,10 31:11,12 33:25 34:15,16,20,21,25 40:9,10 41:22 43:8 56:10,21,22 57:5,6 61:13,23,24 66:13 66:25 67:4 73:15 78:24 86:17,18 95:17,21,22 97:24 114:1,5,9 118:12,13 119:13,17 123:19 125:1 127:10 128:18,24 130:22 132:2 133:1,8 134:3 140:24 141:3,14,23 142:1,7 148:8,9 150:5 151:2,3 155:5 155:9 156:11,19,20 157:5,8 161:1,8,11 161:13,22,23	selection 68:4,5
Schaefer 1:11 2:2,16,20 3:12 5:2,7,17,18 8:10,22 12:11 13:2,4 14:22 15:1 16:15 22:3 36:1 52:8 64:5 71:19 89:25 131:9 169:19 174:16	scores 130:22 131:1	screen 94:24	semantic 73:15
	scoring 115:15 125:24 126:11	screening 48:6 53:14	sense 88:11
	sea 77:7	search 96:12	sensitivity 177:8
	second 119:16 120:2 133:20 143:21 161:6		sentence 86:12 161:13 164:7 165:5,10 182:9
			separate 35:8 93:10

separated 66:7,23	215:10,13,15,21 216:5,9,10,14,14	sets 202:21	shown 13:8 14:24 51:6
separately 189:17	sequenced 91:20 150:23 152:12 186:12 194:7	settling 22:21	57:25 61:22 62:5,23 66:19,21 70:13,19 112:1 113:10 133:12,15 134:20 137:2,4,14 138:20 138:22 139:4 141:11 147:17 148:12 155:2 167:13 175:19 176:13,21 180:19 193:22 215:9 218:12
sequence 2:23 24:6 32:1,2,4,5 32:12 33:1 42:15 45:1,5,6,8,12,16 47:5,11,17,20,24 52:16,16,20,22,25 53:5,13,17 59:22,23 60:3,4 65:23 66:8 68:14 70:7 90:6 91:2,24 92:4,8,11 92:21 93:6,11,15,22 93:25 94:1,1,3,8,9 94:15,16 95:12,24 96:23 97:1 98:18,20 99:5,5,7 101:11,12 101:14,15,17,17,20 102:1,24 103:2,4,6 103:7,10 105:8 106:6,13,15,18,22 107:6,10 108:22 109:21,22 110:8 111:23 112:16,18 112:21 122:24 123:24 125:15 126:2,4,7,8,17 127:19,20,23,24 128:2,22 137:13,16 137:20,20,21 138:5 138:17,18,19,25 139:6 140:4 144:16 145:13,13 148:18 150:12 151:2,5 152:8 157:10 158:10 159:15,17 159:20 168:22,24 171:2 172:2 175:13 186:9,12,20 187:5 187:10 193:8,9 194:1 199:15,25 200:9,16,23 201:2,2 201:20 202:1 211:13,20 215:5,5,6	sequences 19:13 24:16,18 32:16 46:12 47:16 48:3,7 48:8 52:19 59:25 67:15,17,18 90:22 96:18 97:2 99:13,15 99:15 101:24 103:14 104:4,8,10 104:12 106:24 108:3 109:9,11 110:7 111:12 117:13,14,23 138:12,13,13 140:7 148:15 159:16,17 186:5,14,16,17 187:12,18 193:16 199:9,18 213:6	Sf9 59:18,24 60:7,13 62:5,9,23 79:7 206:1	167:13 175:19 176:13,21 180:19 193:22 215:9 218:12
	sequencing 91:18 137:2,25 139:4 148:13 149:1,2 150:3,10,22 151:1,4	shaded 112:10	shows 30:24 56:25 63:24 111:15 114:7 134:8 154:14 176:7,8 180:8,14 186:15 191:21
	sequentially 68:8	shading 119:16	Shrugs 8:5
	series 6:20 106:10 129:6 150:17 183:1 184:17	share 195:5	Shun-ichiro 26:7
	serine 119:13 141:11 142:11 148:7,16,16 190:2 191:12,20 194:3,8,11,15,25 195:3,5,10	shares 152:7	sic 9:24
	serve 103:18	SHEET 221:1,7 222:1 223:1	Siddhartha 11:24
	server 124:21	shell 75:16 77:1	side 115:9,10 127:7,15 141:23 142:1 148:24 173:20,20
	services 4:16 10:18,20	Shon 5:23 8:25 90:3	sign 13:15 15:12
	set 115:19 191:22 204:7	shon.lo@morganle... 4:11	signal 167:25
		short 52:3 96:16 102:3,4,6 102:7 104:23 109:2 140:5	signature 13:12,13,14 15:8,10 222:23 223:23
		Shorthand 3:19 4:14,14,15,15 220:5	signed 13:17 36:20 37:13,24 38:7,10 221:8
		shotgun 91:18	significance 120:18 121:1 148:10 148:11 209:22
		show 51:4 57:19 59:15 61:5 66:16 84:2 87:22 103:3 111:24 127:5 175:17 177:1 182:20 187:1,16	significant
		showed 50:9 59:9 60:4 63:13 200:7	
		showing 174:10 194:12	

120:5 177:13 significantly 20:20 160:24 signing 15:15 43:13 similar 9:17 36:6 37:7,16 65:23 77:15,18 80:24 81:12,15,18 82:2,8,8,19 111:18 111:19 114:4,21,25 116:18,22 117:14 118:10 126:4 129:10 135:3 144:14 152:3 169:4 169:4 172:21 173:21 177:8 182:11,14,17,21 193:13 195:6 209:6 209:8,9 215:8 218:8 similarities 116:16 135:20 192:21 similarity 118:7 147:8 170:15 170:20,24 171:6,16 185:7 similarly 80:25 81:14 148:21 202:24 simple 51:15 104:18 117:6 simply 47:12 67:15 69:13 110:11 116:13 122:17 125:10 160:12 162:9 165:5 166:22 170:2 181:1 187:13 188:9 204:7 204:18 Singaporean 17:17 single 70:13 71:16 72:19 101:5 103:17 121:3 121:10 136:6	177:24 211:14,14 211:20 213:20,20 sir 5:19 24:20 50:21 63:11 sit 13:23 site 71:14 139:1,11,17 140:15,17,21,24 142:12 145:11 190:3,11,12 191:12 191:13 192:13 193:4,18 sites 71:4 111:24 138:9 150:14,17,20 190:4 192:14 193:11 site-specific 150:15 sitting 15:21 38:18 47:3 63:22 76:12 six 109:16,16,21 146:22 size 115:9 184:21 skepticism 209:25 skill 20:4 25:23 26:3 27:8 31:14,16,20 33:3 91:1 96:16 117:21 147:7 217:25 218:4 slight 67:9 180:19 slightly 36:7 76:20 110:11 slow 65:19,21 110:14 slowly 66:4,5 small 19:8 97:17 161:20 181:11 sodium	54:18 56:19 60:18 61:1,9 63:15 75:25 202:14 203:1,10,14 solid 19:12 135:6 soluble 198:2 solution 59:6 63:15 64:1 75:24 79:25 178:22 179:13 197:16,16 197:24 198:4,11 solutions 56:18 76:15 77:4,6 156:5 178:7,10 somebody 82:11,12 85:8 somewhat 59:3 66:21 128:16 146:24 178:17 sophisticated 116:11 sorry 27:11 72:5 91:13 113:3 114:16 137:23 153:6,11 161:5 162:1 173:22 176:16 206:13 sort 33:20,24 42:17 43:15 46:22 74:25 75:6 76:14 82:24 97:15 113:1 122:12 123:16,19 133:16 148:6 161:3 166:18 172:2 179:24 180:8 180:10 183:3 184:13,14,16 199:14 201:3,5 208:2 sound 21:8 sounded 37:16,18 sounding 9:17	sounds 21:5 30:3 38:21 85:6 142:14 source 103:20 106:18 157:17 163:25 175:20 sources 175:22 177:14 178:3 178:4 space 111:20 spaced 129:7 speak 96:3,10 108:8 121:10 188:15 189:12 213:23 speaking 10:1 79:6 83:20 188:8 speaks 191:16 species 17:6,12,18 22:12 32:16 46:12 48:14 50:10,20 51:7,8 52:23 59:20 65:23 66:7,17,20,23 67:2 68:20 69:11,21 74:1 74:1,2,7,18,19 75:2 75:8,16 78:2,10 80:24,25 81:12,15 81:20 82:14 84:4,7 84:15,18 85:3 86:21 87:10 88:6,16 98:10 98:11 110:19 111:12 112:4,13 122:2 139:12 142:22 144:11 155:23 161:10,20 162:3 165:2,8,10,12 165:19,22,24,25 166:13,14 170:2,7 170:24 171:15 172:24 177:5
---	---	---	--

184:24 192:25 199:5 214:16 species-based 166:22 specific 9:7 19:15 24:14 33:21 34:11 42:21 45:5 48:14 50:8 55:19 57:22,24 59:5 59:15 63:20 75:23 76:5,5 78:12,23 79:25 91:11,17 99:17 100:1 107:25 117:1 121:16 126:20 143:19 145:20 149:3 150:14,16 151:16 152:11 156:5,12 158:20 171:7,10 173:7,10 175:20 176:12,20 177:23 185:5 187:7 196:12 197:18 199:21 210:21 213:10,22 specifically 7:20,24 20:3 28:5 43:2,10 45:16 46:16 46:23 47:10,11 48:13 50:11,12 51:4 57:16,25 58:19 59:4 63:18 64:4 76:24 87:22 90:13 91:24 92:13 100:16 136:16 147:2 156:4 189:1 195:19 specification 44:19 118:18 217:24 specificity 191:18 192:4 193:22 195:8 specifies 203:21 specify 113:8 spectrum 71:13 108:16,17	124:4 speculate 53:10 61:24 142:15 166:12 194:23 speculating 166:21 speculation 53:19 162:17 163:9 166:23 200:12 speculative 162:7,15 170:6 spell 5:15 spelled 179:11 spire 114:21 splicing 100:23 spoken 11:11,13 12:4,13 218:21 spot 95:1 SR 98:19 SRA 90:14 102:17 SRA's 91:10 SRR610305 95:16 stand 29:15 78:7 169:16 196:3 standard 14:16 42:12 48:6 85:4,12,14,22,22 86:16,22 89:16,18 89:19 107:1,20 164:23 184:10 217:12 standardized 42:10 179:4 standards 85:18 89:2	start 34:14 57:18 136:1 139:23 started 99:12 starting 99:4 106:14 137:16 185:22 starts 86:12 119:13 state 3:17,20 5:15 44:24 94:5 124:5 220:6 stated 31:23 45:15 46:10 165:5 statement 20:6 29:15 32:6 53:3 53:9 73:22 139:3 143:21 182:9 192:15 200:7 201:1 206:24 207:2 211:6 211:16,23 statements 13:20 39:11 88:20 121:9 187:21,25 188:4,5,13 189:5 207:10,13 208:7 209:9 210:17 211:10 STATES 1:1 3:1 statistically 177:13 step 67:19 125:5 steps 56:7 104:14,16,18 106:5 110:12,13 stick 61:3 79:22 185:1 stilted 10:3 stimulating 41:23 stimulation	81:11 STIPULATED 3:10 straightforward 31:25 107:19 117:4 187:9 208:16,21 strain 72:6 strategies 106:10,12 strike 37:25 41:17 69:8 79:11 112:14 150:7 171:4 185:18 209:24 213:25 218:14 strong 81:21 82:5,7 99:22 strongly 111:18 114:4,25 structural 71:6 structure 68:24 120:13 123:20 123:24 124:3,11 125:7,12 127:18,25 128:3,7,16 130:23 141:1,21 142:3,7 143:8 211:1 structures 124:1,24 126:24 128:4 129:17,18 130:10,13 141:14 141:24 students 14:13 studied 36:8 74:8 100:21 132:12 studies 20:16 70:21 153:1,4 173:9,18,18 study 39:20,22 70:21 132:18 144:3,8 145:2,3,5 156:18
---	---	---	---

165:17 167:17 168:5 172:17 180:1 182:10 191:18 studying 30:13 37:22 38:15 81:2 144:18 subcomponent 125:12 subject 218:6 subjective 79:21 submit 32:18 submitted 6:21 25:10 26:19,23 28:13 105:3 209:2,5 submitting 36:24 subscript 148:7 subsequent 21:18 145:12 substance 8:22 52:11 90:2 218:22 substantively 44:18 substitute 36:5 37:16 194:15 substituted 139:24 substitution 71:12 112:11 140:14 141:10 143:3 substitutions 71:17 113:15 139:23 substrate 41:8,9 77:2 83:19 190:4,12 191:13 192:3,13 193:21 195:8 substrates 191:23 194:12 subtle 127:13 161:19	subunits 133:6 succeed 109:3 success 107:14 108:5,7,20 successful 108:21 successfully 117:12 177:2,18 214:15 suddenly 108:12 215:14 216:13 suggesting 19:18 152:11 suggests 160:15 sulfate 56:20 60:20 61:2,12 62:17 63:4,15 sulphate 54:20 summarize 71:11 summarizing 213:22 summary 97:14 177:11 summation 155:2 superficially 127:9 superior 58:17 60:11 supernatant 198:4,5,7 superscript 148:7 supplemental 139:13 145:10 Supplementary 133:13,16 supplied 87:5 supplier	87:4 suppliers 86:13 87:2,21 supply 10:17 support 31:10 44:9,13 214:21 supporting 26:2 suppose 44:24 supposed 163:8 sure 6:12 9:18 31:2,21 42:22 77:24 87:17 105:22 110:22 117:17 121:8 126:21 131:4 138:15 140:22 141:6 149:24 176:17 183:3 186:23 190:15 202:16 213:12 surety 192:1,6 surprising 66:22 194:6 Surveillance 2:12 survival 67:24 68:2,3,7 69:21 69:24 70:9 75:1,8 76:1,6 survive 76:16 suspect 120:5 switch 89:21 sworn 5:3 220:8 system 20:16 72:16 75:11,13 115:15 116:12 126:11	systematically 161:21 S-C-H-A-E-F-E-R 5:18 T table 133:13,16 134:16,19 135:13 136:10 176:7 Tachypleus 17:12,14 45:6 46:6 48:1,11,13,22 49:20 49:24 50:9,18 51:6 52:17,18 56:13,24 59:10,12 61:5,17 74:13 99:6,13,14 100:10 101:8,12,12 101:14,15,20 102:23 103:9 104:4 106:18 110:20 111:13 112:7 114:8 120:8 124:24 125:24 126:13,18 126:25 127:5,15,19 133:5 134:1,7,21 135:9 136:12,18 137:10 138:14,17 139:1,17 142:9 144:4 145:5,7,18 146:1,7,12,17,22 163:12 171:23 172:8 173:24 190:5 191:19,23 197:5 210:25 213:7,14 Tachyplus 194:10 take 7:10 52:3 67:19 71:19 89:22 96:16 101:16 106:1,22 110:11 131:4 135:20 138:4,16 139:20 150:11 156:12 164:23 168:25 174:3,13
--	---	--	---

181:12 183:7 188:9 198:19 206:23 210:9 218:16 taken 1:12 3:12,15 52:6 89:23 106:5 131:7 174:14 198:21 218:17 220:9,13 221:4 takes 110:15 164:8 185:8 take-home 135:17 TAL 62:10,23,25 79:2 84:8 87:21,23 88:19 talk 23:11 24:5 29:22 42:15 48:17 56:15 58:22 64:18,21,23 65:13 84:25 86:19 90:5 108:2,18 132:4 132:7 161:15 175:12 197:22 199:8 talked 104:2 169:23 184:16 207:9 208:6 talking 17:7 24:8,9 43:2 52:14 54:1 55:14,16 55:18,19 57:16 67:12,14 69:13,14 69:15,20,21 70:6 71:14,23 73:7 82:8 83:12 84:22 86:25 87:1,9 88:15 89:2 90:10 93:24 98:8,12 98:15 105:16 106:6 110:21 113:20 114:11 117:7 118:16,24 119:9 122:3 141:6 143:11 154:9,10 170:20,22 171:16,16 172:15 173:8 175:4 183:11	183:12 185:17 195:18 196:13,15 196:19 197:13 199:13 200:12,25 201:21 210:4 215:25 talks 16:1 65:1 target 108:22 150:12 task 110:1 tblastn 99:3 101:16 TCT 187:24 teach 35:10 teaches 206:12 team 39:4 96:11 technique 30:12 110:12 137:15 137:18 166:9 techniques 21:17 48:5 98:11 technology 188:11 tell 5:3 7:5 38:18 39:7,10 44:23 78:23 87:23 88:21 124:10 206:10 telling 192:10 tells 7:24 172:2 template 124:25 125:3 tend 68:22 82:6 163:2 ten-minute 198:19 term 51:11,13 79:14 81:18	185:5,7 203:24 206:9 terminal 167:21 terminology 20:8,9 40:20 terms 9:11 16:17,21 49:12 72:18,25 77:15 82:25 163:13 176:14,22 201:1 204:15 211:1 217:7 tertiary 128:3 test 84:11 87:7 89:8 95:3 178:22,24 183:23 tested 155:18 177:25 testified 5:4 6:9 37:13 91:22 testify 6:4 testifying 43:13 54:25 testimony 6:7,21 8:4 11:21 12:8 12:23 19:17 20:5 23:10 52:12 57:8 90:3,19,25 91:7 96:15 117:20 126:23 131:12 176:21 192:10 218:22 220:7,8 testing 23:6 84:9 144:24 175:9 179:12 tests 86:14 text 33:21 40:6 60:22,23 67:4,6 86:10 87:22 88:8 133:9,11 169:16 196:3 textbook 116:7	Thank 65:6 94:17 131:11 136:25 theorized 201:9 theory 201:14,16,17,18,22 201:22,24 thereof 212:7 thereto 220:15 thesis 18:6 20:18,20 21:1 21:17,24 30:25 92:18 thick 154:19 thing 19:3 82:17 83:13 86:25 107:11 115:7 129:15 141:7 180:22 181:12 185:18 215:2 216:19 things 25:10 29:16 42:7 66:5 67:21 77:3 79:18,20 82:3,4 94:8 105:10 106:25 108:19 120:23 127:22 142:6 158:9 167:24 170:19 179:25 183:4,11,18 190:19 191:25 198:8 200:14 207:8 208:10 215:14 218:9 think 11:3,14 12:7,22 21:6 23:8,25 30:1 34:1 34:14 38:16 51:2 62:15 63:20 64:9,16 66:14 67:13,20 71:14 77:17 78:22 84:13 88:2 92:1
--	--	---	--

93:17 95:15 97:10 105:11 116:21 119:6 127:21 130:17,25 131:17 133:1 134:11,14 137:24 139:19 140:6 141:15 143:14 144:7,20 145:21 147:11 149:5,18 153:2 154:18,19 156:15 158:19,21 167:3 175:2 179:19,23 184:22,24 187:2,6 208:6 210:13,14 212:13,25 219:3 thinking 24:2,3 53:21 141:7 185:13 third 114:15,16 119:12 129:1 third-to-last 114:3 Thorne 2:22 thought 35:25 58:14 105:25 169:20 173:22 208:15 thoughts 198:20 thousand 184:22 Thr 133:20 three 17:6 25:10 26:11 66:23 74:2 93:9 107:4 111:12 121:24 139:7,22 140:1 190:2 192:1 192:11,24 195:9 threonine 133:20,21 threshold	61:12 63:8,9,10 84:23 118:11 160:13 202:21 203:3,6,7,14,15,19 203:20,24 204:2,5,6 204:18,19,20 205:19 206:9 thresholds 61:7 82:19 115:14 thrust 37:20 38:12,25,25 39:12,12 54:2,5,7 54:25 55:2,2,6 time 10:1 18:10 23:2 24:3 24:3 30:9 37:15 51:18 65:19 66:8 68:11,14,21 71:20 74:12 85:13 87:6,6 91:5 101:5,25 104:23 109:2 112:6 117:12 118:6,12 130:6,16,24 143:5 143:10 146:21 147:17 159:12 190:14 201:15,16 209:9,12,17 215:3,8 216:19 times 58:16 83:9 164:11 timing 23:22 Tina 11:5 34:6 titled 56:16 TN 4:15 today 5:8,13,21,22 6:4,7,19 6:21 8:3 13:23 15:21 16:11,18 17:7 17:19 23:11 38:18 39:7 43:13 47:3 57:8 63:22 76:12 131:15 218:23	Tokunaga 2:11 47:11,15 106:23 110:7 131:17 132:1 132:4,11,14,21 133:9 137:1 138:25 139:4,15,20 143:18 143:19 144:9,18,22 145:11,17 147:7 150:22 151:8 163:17,19 173:11 173:23 174:4,5 190:16,18,22,23 191:16,18 193:2,7 193:25 195:14,16 195:18 Tokunaga's 137:25 163:12 tolerance 184:7 tolerated 68:25 69:2,5 121:21 tomorrow 219:4 tools 119:2 top 68:6 86:11 99:13 123:8 130:15 141:8 159:3 160:5 166:20 217:9 topics 21:24 top-scoring 126:15 Toshio 208:3 total 134:4 135:4,22 136:17 144:8 touched 20:20 trace 105:12,17,19,20 TRADEMARK 1:1 3:1 train	105:24 training 21:2 24:19,21 29:1 transcribe 9:25 transcribed 102:9 transcribing 8:3 transcript 11:20 19:2 101:9 103:21 221:4 transcriptome 95:13 transferred 38:14 translated 32:5 transmitted 72:12 tremendous 167:11 triad 190:4,11 191:13 192:2,6,13 193:4 194:1,2,9 195:6,10 195:15,18,20 TRIAL 1:2 3:2 trick 42:1 tridentatus 17:13 49:20 127:15 127:19 190:5 triggered 77:1 triggering 83:22 trivial 82:3 96:23 true 6:6 15:18 30:16 46:22 63:1 150:7 189:6 192:15 196:25 203:18 206:18,19,24 207:2
--	---	---	--

221:5	25:10 26:15,17	unaware	units
trust	32:15 57:22 60:14	181:24	199:3
181:1	77:3 81:25 82:14,20	unclear	universe
truth	93:9 99:18 100:5	209:21	166:5,14,25 169:21
5:3,3,4	103:14 106:25	underneath	169:24
truthfully	110:19 111:16	111:20 113:14	university
6:4	112:3,12 115:2	understand	10:17,19,20 90:15
try	120:15 122:1 127:3	5:25 6:2,3,5 7:4,5,8	95:14 106:13
32:18 71:2 100:6	127:6,7,10,22	7:17,18 16:24 32:11	112:22
146:24 155:18	128:13,17,18	37:6 44:21 45:7,18	unknown
trying	129:14 133:5	46:7,14 49:16,17,21	143:4,8,8 167:8
79:17 82:22 121:5	136:16 144:5,10	50:6,19 51:5 52:24	unnamed
126:22 136:22	147:3 152:10,16	55:3,7 66:1 79:17	177:24
181:7 192:9 204:10	154:17 155:10,12	80:23 82:23 83:20	unpatentable
Trypotan	155:16,19 159:6	90:19 104:22	36:3
151:21	161:10 165:23	122:21 126:22	unpublished
trypsin	167:6 170:8,19	136:8 139:16	170:24
138:5 150:13,14,15	171:15 172:20	164:25 181:7,20	unreported
150:20 151:10	174:3 176:9,17	192:9 204:10	103:24
174:7 191:22 192:5	177:12 178:3,3	217:18,22	upper
194:13	180:14,16 183:11	understanding	204:3,12,16
tryptic	183:13,17,22	16:20 25:2 29:6 35:3	upstream
47:10,16 138:1,2,3,9	184:24 188:19	36:5 44:6 51:18	129:14
149:19,21 150:3,9,9	191:25 203:22,22	54:6 58:24 60:1	use
151:1,4 159:15	204:6,15 215:1,3	72:18 85:5 88:14	16:18,21 17:18 31:24
160:10	216:7	90:25 92:9 100:11	41:3,12 42:12 48:2
tryptophan	type	156:1 175:24	49:9 53:13 54:5
141:16	19:24 25:19 41:16,19	176:15 206:3 214:6	59:1 65:22 77:15
tumors	41:19,22 43:14 92:5	217:2,16 221:7	79:14 80:10 81:22
18:15	98:24 126:12	understood	82:6 83:8,9 84:8,8
turbidometric	135:18	7:7,9 8:1,8,24 17:5	87:13,14,17 88:24
175:22 176:5 178:5	types	18:10,25 30:14 31:8	89:6,13 101:6,25
turn	71:21 98:1 104:11	45:20 46:24 81:9	103:5,6,11,13
13:10 17:21 25:20	typewriting	90:20 128:20 167:2	106:11 107:2,6,13
40:8 56:1 86:9	220:10	167:4 170:25	108:1 109:25 110:6
202:2 213:12		174:12 178:20	112:16 117:9,24
turned		undetermined	119:2,6 135:19
216:24		18:7	170:14 182:14
turning		unethical	199:10 206:9
148:4		14:14	210:20
Tween		Uninformed	useful
154:18		10:20	124:10 185:7
twins		unit	uses
183:12		133:6	40:24 116:10 127:24
two	ultimately	UNITED	181:21 212:7
6:22 8:15 12:24	183:21	1:1 3:1	usually

100:22 117:11 138:3	10:10,12 verbal 8:5,7 verified 106:16 verify 13:19 34:2 96:4,8 109:19 157:11 version 38:21 116:24 117:1,5 117:8,15,16 versus 58:18,18 60:12 79:25 82:17 85:14 87:21 87:23 102:13 115:8 116:9,12 117:7,18 118:14,14,19 119:5 128:10 129:8 134:17 136:20 138:14 140:2,25 142:8 146:1 166:6 166:17 170:4 172:16 178:7 179:1 179:3 200:14 vicinity 140:17 view 26:2 34:18,24 92:25 114:24 122:23 180:13 183:20 189:15 196:7 viewed 209:12 views 163:2 virology 20:19,21 virus 2:12 18:5,8,17,19,20 18:22 20:14,14 21:22 72:6,7,10,11 72:11,16 73:1,9,12 98:15 viruses 71:15 72:3,3,4 vitro	76:9,22 vivo 76:10,23 VOLUME 1:15 vs 1:6 3:6 VWW 119:17	106:10,21 107:20 108:19 114:2 126:6 129:7 141:24 142:25 143:1 145:16 147:4 151:14 160:11 166:7 170:14 179:7 200:13 212:14 ways 40:21 167:7 187:9 208:16 211:17 weakly 111:19 website 94:24 weeks 109:16,21 110:16 weight 193:14 Welcome 131:9 went 30:4 104:14 wet 42:17 43:8,12 we'll 7:10 11:4 17:7 33:1 41:12 42:14 52:4 67:9 77:18 105:23 129:11 we're 6:19 8:6 16:16,17,20 23:11 58:20 66:19 67:14 69:13,13,15 69:20,21 70:6,17 71:23 73:7 78:3 80:20 83:12,15 86:25 87:9 110:4 113:20 117:7 118:15,24 119:9 122:3,6 128:5 141:6 141:24,25 142:2 143:11 148:19 149:20 154:9,10 156:2,3 168:19 170:20,21 171:16
V V 140:12 141:15 vaccine 71:24 72:6 vague 42:20 59:3 72:20,21 72:22 78:21 126:19 211:10 213:18 value 63:8,9,10 96:5 103:18 160:17 180:9 202:21,25 203:3,6,14,15,15 204:7 210:9,16 values 84:10 147:25 178:21 variables 85:17 variant 99:1,9,17 100:4,9 101:5 102:5,11,13 102:14,18,20,21 107:22,25 variants 99:19,24,25 100:5,14 100:15,23,24 101:23 102:1 103:24,24 variation 122:1 138:11 variety 42:6 66:2 87:3 186:18 187:8 various 71:2 115:20 153:25 156:8 162:12 181:25 183:20 varying 150:19 vast 195:22 vendors	W W 117:16,17 140:12 141:16 Wacker 3:17 4:10 wait 9:23 10:4 114:10 want 9:23 13:23 15:22 16:12,20 30:23 43:5 46:15 85:24 86:9 87:16 90:24 105:24 106:1 108:6,21 136:8 150:12 154:3 162:4 194:23 198:19,25 205:18 wanted 19:19 34:2 wants 163:4 206:7 Wan-Shon 4:9 waste 101:4 water 59:8 77:6,7 80:1 way 27:21 30:15 31:22,22 33:8 37:11 38:11 44:24 49:9 50:6 51:10 60:21 75:18 77:15 79:20 83:14 84:17 88:25 102:4 102:14,17,19 103:16 105:12		

173:12 182:20 183:11,12 185:17 199:13 200:12,25 201:21 210:4 215:25 we've 51:25 89:2 105:16 113:14 118:1,8 131:2 187:2 196:19 197:13 207:22 whatsoever 6:8 11:19 12:18 180:23 wild 72:7 willing 157:22 witness 8:24 13:8 14:24 39:24 43:21 65:7 70:19 86:3 95:9 111:4 124:16 131:21 149:9 168:8 179:17 191:4 207:19 220:6,8 Wolf 4:3 5:11 word 49:10 54:5 55:2,2,11 55:12 80:5,7 81:13 81:21 82:5 87:13,14 87:17 88:24 136:17 170:15 173:13 187:25 188:1 192:19,20 wording 61:3 words 38:3 51:20,21 54:1 59:2 76:20 80:9 92:2 189:21 207:15 216:1 217:25 218:2 218:9 word-for-word 54:21 55:1 work	14:6 19:16,23 20:3 28:17 30:5 81:2 96:20 132:16 136:5 153:18 183:5,18 195:6,11 worked 10:23 22:14,23 25:12 64:11,13,14,16 98:9 118:4 working 14:13 23:1 27:14 84:20 157:20 158:3 158:8 178:21 works 10:10 126:6 world 44:23 76:10 209:3 wouldn't 53:16 110:6 147:14 216:10 wow 172:3 write 101:2 133:3 writing 163:3 written 14:1 31:9,18 44:8,13 63:6,8 162:9 169:17 196:3 205:23 214:7 214:20 217:1,12,22 wrong 184:5 wrote 13:25 14:5 37:15 39:2 50:5 209:17,17 209:18 X X 146:20 148:6,7,19 Xes 148:10,11 Y Y	146:23 yeah 40:15 42:1 76:19 78:6 79:19 86:12 91:14 95:15 104:20 111:10 116:15 119:18 145:21 149:25 152:15 156:1 158:22,25 159:3 161:6 182:8 199:1 210:6 211:16 year 9:6 years 30:11 66:11 67:1,8 67:10 81:7 104:25 118:14 130:3 210:24 Yep 34:13 67:5 114:14 190:25 yes-but 69:4 yes-or-no 50:25 yes/no 69:3 89:10 yes/nos 84:11 Yukon 24:7,15,18 91:11,15 94:19 Z zero 100:25 181:13,14 zoom 140:24 ZW 154:18 zwittergent 153:7 154:18,21 zymogen 19:6,20 20:3 23:13 42:24 43:2 46:1,18 86:20 91:12 93:11	98:5,7 143:22 163:24 190:2 192:11 \$ \$800 14:19 0 001 154:25 155:17 005 155:4 02210 4:5 084-004533 220:21 1 1 1:15 13:12 14:15 15:9,13 44:13 62:13 84:3 154:14,23 1st 96:13 1.2.4 116:24 117:2 10 31:6 54:17 60:17,25 61:11 84:3 86:10 109:14 144:20 202:22,23 203:4,13 203:17 204:23 205:5,12 10th 32:3 33:14 10:20 52:5 100 6:12 108:9,18 109:3 130:15 139:14 185:13,16,24 203:10 204:24 205:5 1001 2:6 39:24 40:2
--	--	--	---

1005 2:7 207:18,21 1006 2:8 43:18,21 70:19 1007 2:9 190:25 191:3 101 174:18 179:15 205:3 1016 2:10 191:3,6 1019 184:24 1020 184:25 1022 2:11 131:20,25 190:16 104 186:3 1066 2:12 70:18 71:9 107 202:3 109 8:18 12:17 44:4,14 44:19 154:1 188:20 208:4 11 62:25 202:14,22 11,236,318 1:7 2:6 3:7 13:3 11,959,109 14:23 11:20 52:5 110 3:16 4:10 146:12 111 2:22 119 34:14,15 12 1:13 3:15 63:1 86:10 88:4 130:3 210:22 124 2:23	125 214:12 13 2:15 13th 34:9 130 66:25 131 2:11 14 62:22 149 2:13 15 2:19 54:18 60:18 61:1,13 63:3 150 67:1 146:22 152 163:23 153 163:21 156 2:14 133:13 16 54:19 56:20 60:19 61:2 63:4 211:25 168 2:17 177 2:7 179 2:21 180 114:2,12,13 186 213:12 19 62:22 190 2:9,10 1980s 74:5 120:20 1990s 24:4,4 74:6 143:11	1991 2:11 106:23 110:7 132:1,16 135:5 1995 17:24 30:1 2 2 17:22 57:17,18,19 62:16,23,24 125:4 133:13,16 145:23 152:6 168:15 175:7 180:20 2.2 2:24 124:20 126:7 20 61:14 62:17 65:11 154:19 180:21 203:13 210:24 221:9 2003 159:9,12 169:9 2006 152:3 159:9,13 169:10 2007 2:10 21:4 2009 152:3 169:7,12 2012 74:12 118:14 2013 31:6 32:3 33:15 34:3 34:5,9 73:24 77:25 90:7,20,20 91:25 94:7,20,25 95:20 96:1,9,13 102:16,19 102:20,22 104:3 105:14,17,20,21 109:10,14 117:21 129:20 130:12,20 133:4 143:5 167:2,3 174:24 188:11 189:18 196:9,18 197:1 198:13,14 208:25 215:12,22	2016 188:8 189:17,23 208:24 2019 214:14 215:4,14 216:13 2025 13:12 15:9,13 130:1 130:10,20 2026 1:13 3:16 2035 2:13 149:7,8,11 150:3 2036 2:14 152:3 156:16 164:14 2038 2:15 13:1,5,8 15:2 2044 2:16 65:4,7 2049 2:17 152:6 168:7,11 2053 2:18 95:4,8 206 146:17 2062 2:19,20 14:21,24 85:25 86:2 2075 2:21 179:14,15,16 2081 2:22 111:1,3 113:16 21 31:5,10 33:14,18 34:1,18,23 35:10 36:3,6 37:7 38:2,4 38:13,13 39:1,2,6 39:13,15,20,22 40:9 40:24 41:15,18 44:9 48:12,13,24 49:13 49:23 54:1,7,8,9,10 54:18,21,25 56:9,19 60:14,18,21,22,23 61:1,8 62:13 63:4
---	---	---	---

63:21 66:11 67:8,11 202:5,9,11,15 205:8 205:10,14 214:18 215:22 2100 2:23 124:14,15 22 36:2,5,12,19 37:3,6 37:12,14,16,21 38:1 38:3,7,10,12,14,20 38:25 39:2,3,5,8,11 39:12,14 54:2 55:23 55:23 24 73:19,19 78:4,5 80:17 25 61:11,14 62:17 26 78:16 293 54:15 56:8 206:13,13 3 3 107:3 108:3 164:16 175:15 176:3,13,21 177:24 212:1 3-D 123:16 124:19 127:18 3-dimensional 120:7,9,10 123:23 124:24 126:24 30 97:11 31 109:10 31st 95:19,25 318 8:16 12:17 26:12,20 31:6 39:20 40:2,6 40:17 41:11 44:4,19 51:12 133:1 154:1 188:20 201:8 202:5	208:4 214:3,3 219:1 34 149:24 168:10 169:16,17 35 128:22 39 2:6 4 4 134:25 152:4 159:3 161:4,5 175:15 217:13 4:55 219:9 400 97:15 43 2:8 46 25:20,22 112:25 113:4,5,7 119:12 47 26:1 48 29:3 490 207:17 498 2:7 34:19 93:18 105:16 112:19 187:22 188:20 207:10,22 210:4,7 5 5 2:4 30:16 57:17,18 57:19 61:9,21,21,24 66:15 88:4 107:3 108:3 159:3 164:16 177:12 180:4,4 52 31:4 53.6 133:22	56 56:1 57 56:15 58 34:14 214:3 59 133:25 6 6 66:16 154:20,22 155:16 600 4:5 97:16 60606 4:10 61 34:22 133:1,3 629 93:19 94:13 64 65:12 66 2:16 90:23 670 188:2,25 676 207:4 214:21 7 7 61:5,16 77:13 78:14 153:19,19 7S 137:2 138:13 145:10 148:4,13 193:10 70 2:12 707 127:5 74 106:2 767 2:8 31:7 43:19,25 44:17,25 45:4 47:4	50:1 52:14 56:5 63:12,23 77:12 104:3 115:16 205:23 206:10,12 207:7 78 106:2 108:1 8 8 15:25 8S 148:4,5 193:10 85 65:12 199:2 86 2:20 199:1 87 190:1 194:19 195:24 196:4 199:1 89.3 152:5 157:4 160:8,15 169:1,10 9 9 44:14 61:23 62:2 168:16 9-and-a-half 185:3 9:02 5:1 90 151:2,15,18 158:15 160:12,15 168:20 169:10 184:18,20 185:19,22 90.5 152:8 168:16 169:2 169:13 171:1,6 172:1 175:13 185:2 900-smething 185:19 920.4 134:6,25 135:14 136:17,18
--	---	--	---

95 2:18 95.6 146:11 98 124:22 99 202:25 99.4 130:15 99.8 130:15 99.9 130:15,15 994 134:7 135:14 136:18 136:19			
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